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**A TEXT-BOOK OF ORGANIC CHEMISTRY**



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TORONTO**

**A TEXT-BOOK**  
**OF**  
**ORGANIC CHEMISTRY**

**FOR STUDENTS OF MEDICINE AND BIOLOGY**

**BY**  
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**New York**  
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## PREFACE

IN preparing this text-book the aim has been to restrict its contents to a degree which should make it suitable for a course continuing through a half of an academic year. The book embodies the substance of the discussion of organic chemistry presented with the author's course in the chemistry of nutrition during the last eight years, and emphasizes the biological rather than the synthetic and technical viewpoint. It is hoped, therefore, that it should serve as a satisfactory text for students of medicine and others who can give but a semester to this subject, and whose interest is in some field of biology.

The text-books ordinarily placed in the hands of students contain more matter than can be assimilated in an academic year, and make necessary some omissions. They reflect the special interests of their writers in extending the subject matter relating to methods of synthesis, with an undesirable multiplication of individual compounds described, or in restricting these and extending the description of technical processes. It has not infrequently been the case that in text-books designed for medical students the other extreme has been reached, and wholly inadequate evidence has been offered in support of the structural formulas presented. The book then consists of a description of

the biologically important compounds, burdened with formidable formulas in which the student sees no meaning.

It is the belief of the author that, if properly presented, the theory of organic chemistry never fails to arouse the interest of a bright-minded student. To be appreciated by the beginner it must be shorn as far as possible of details which burden the memory. The aim has been to present a complete line of reasoning, based upon the properties of the substances considered, in support of the validity of every formula employed. This end has been attained except in the case of the terpenes and a few alkaloids. In all cases the effort has been made to select for purposes of illustration those compounds which have biological importance rather than technical. The course here offered will, it is hoped, serve to fit the student for intelligent work in physiological chemistry by giving him an appreciation of the spirit of organic chemistry and an understanding of the relationships and transformations which go on in the plant and animal world.

Since the book is not intended to serve as a guide to manipulation the usual introductory chapter on methods of laboratory work is omitted. Such information is now readily available in a number of laboratory manuals.

E. V. McCOLLUM.

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# ORGANIC CHEMISTRY FOR STUDENTS OF MEDICINE

## THE FATTY COMPOUNDS

### CHAPTER I

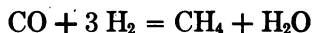
#### THE SATURATED HYDROCARBONS

1. The simplest of the compounds composed of carbon and hydrogen is *methane*,  $\text{CH}_4$ . The compounds containing only these two elements are called hydrocarbons. It occurs widely distributed in nature, in the gases evolved from volcanoes, and in those which escape from coal mines, where it is called *fire damp*, and as the principal constituent of *natural gas*. Coal gas contains considerable amounts of this compound (30–40 %), since it results from the destructive distillation of many kinds of organic matter. Methane also results from the degradation of vegetable matter, especially cellulose, by certain kinds of microorganisms. In this way it is produced by the fermentation of vegetable tissues under water in marshes, and derived its older name of *marsh gas* in this way. It is an ever present constituent of the gases in the intestines and is normally found in small amounts in the respired air, some of the methane produced by fermentation in the intestines being absorbed into the circulation and eliminated through the lungs.

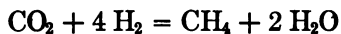
## 2 Organic Chemistry for Students of Medicine

Preparation:

(a) When a mixture of carbon monoxide and hydrogen is passed through a tube containing reduced nickel, heated to 200° C., there is produced methane and water:



(b) At somewhat higher temperatures (230°–300° C.) carbon dioxide is likewise reduced by hydrogen in the presence of finely divided nickel, the latter undergoing no change:



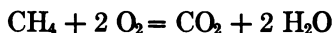
(c) Hydrogen sulphide and carbon disulphide, when passed through a tube containing heated copper, react to form copper sulphide and methane:



Other methods will be described for the formation of methane from certain of its *derivatives* later.

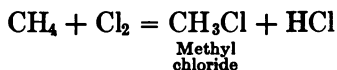
Properties: Methane is a colorless and odorless gas. Its specific gravity is 0.559, air being taken as 1. When subjected to a pressure of 140 atmospheres it liquefies at 0° C. Its boiling point is –162° C. and it solidifies at –186° C. The electric sparks from an induction coil decompose methane into carbon, which is deposited as a black soot, and hydrogen gas. The strongest oxidizing agents, such as nitric and chromic acids, scarcely attack it, and concentrated sulphuric acid and alkalis have no action upon it. It is therefore one of the most stable and inert of chemical compounds. On being led through a red-hot tube it is split up in part into its elements.

carbon and hydrogen, but in part forms more complex hydrocarbons containing carbon chains, which will be described later (6). It burns with a faintly luminous flame. When mixed with air or oxygen it forms a violently explosive mixture, carbon dioxide and water being formed :



This is the reaction which occurs when the *fire damp* of mines explodes.

**2. Formation of Derivatives of Methane.** — Chlorine or bromine react with methane forming respectively chlor and brom methanes. Methane mixed with chlorine is easily exploded. If two atoms of chlorine (one molecule) be present in the mixture for each molecule of methane, the following products represent the principal reaction :



The methane molecule less one H atom is known as the *methyl* group or radical.

*Methyl chloride* is a colorless gas of a pleasant ethereal odor which boils at  $-23.7^\circ \text{C}$ . It is slightly soluble in water (4 volumes in 1 of  $\text{H}_2\text{O}$ ) and can be easily freed from hydrochloric acid by washing. Methyl chloride is used for producing low temperatures artificially. When strongly compressed the volume of the gas is greatly decreased and it becomes hot. If it is cooled as it is compressed until it is under a great pressure and is at the ordinary temperature, and is then relieved of its pressure, it expands again and its temperature falls far below the surroundings.

## 4 Organic Chemistry for Students of Medicine

Water in contact with pipes in which the expansion is allowed to take place is frozen.

Methyl chloride is a good solvent for the *ethereal* oils and is employed for extracting the odors from flowers. Its extraordinary volatility makes it possible to separate the solvent from the extracted odorous substances, which are themselves very volatile.

Methyl chloride may also be called *chlormethane*. Either of these names gives an idea of the nature of the substance and from what mother substance it is derived.

The chlorine atom in methyl chloride behaves very differently from that in the halides of the metals. The latter give with silver nitrate a precipitate of silver halide. Methyl chloride gives a precipitate of silver chloride only very slowly when left long in contact with silver nitrate in solution.

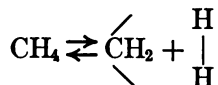
This difference in behavior is due to the fact that in solutions of the metallic halides the chlorine is *dissociated* from the metal to a considerable extent as chlorine ion:



In the dissociated condition the chlorine ion carries a charge of negative electricity, and when a current of electricity is passed through a solution of sodium chloride the  $\text{Na}^+$  ion migrates to the negative pole and the  $\text{Cl}^-$  ion to the positive pole, thus transporting the charges which they carry. They are therefore conductors of electricity. Methyl chloride is not appreciably ionized when in solution, and does not therefore conduct the electric current. Its low rate of reactivity with  $\text{AgNO}_3$  is also the result of

its nearly undissociated condition. In general molecules do not react with each other, but chemical change is usually the result of the property of compounds which causes them to dissociate into simpler parts which are in a much more active state chemically than the molecule from which they were formed. Since methyl chloride does react very slowly with  $\text{AgNO}_3$  it is believed by many chemists to be in a very slight degree dissociated.

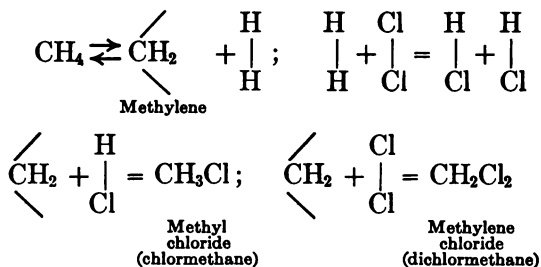
A compound such as  $\text{CH}_4$ , in which all the valences of each of the atoms it contains are saturated, should theoretically show no tendency to react with other chemical substances. The reason why, *e.g.*, chlorine does react with methane is best explained by the theory elaborated by Neff, which postulates a *very slight* dissociation of methane into methylene and hydrogen:



These components are in dynamic equilibrium with each other. This means that any agent which removes one of the dissociation products will induce the further dissociation of a part of the  $\text{CH}_4$  molecules to maintain certain relationships with respect to the three components of the system. Only the dissociation products are active chemically so that the speed of reaction will be determined by the degree of dissociation of the methane. This is greater at higher temperatures than at lower, so that reactions of this sort are greatly accelerated by heat. According to this theory the reaction of methane with chlorine takes place in the following way:



## 6 Organic Chemistry for Students of Medicine



Simultaneously some of the active methylene groups should theoretically react with each other forming molecules with two carbon atoms, etc. This theory is in accord with the observed facts, viz. that the reaction of methane with chlorine does not lead to the formation of a single product, but of several products simultaneously. In representing the reactions between organic compounds among themselves and with inorganic substances, the equation written represents the principal reaction only. Further evidence in support of this belief will be presented later.

### 3. The Geometrical Structure of Methane. —

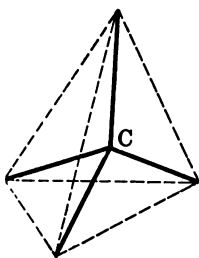


FIG. 1

The experience of many chemists has shown that the relationship which exists between the very numerous organic compounds can be expressed in a very useful way by assuming that the atoms which make up the molecules occupy definite relations to each other in space. The carbon atom is conceived to have its four affinities directed toward the angles of a regular four-sided figure (tetrahedron), the C atom itself occupying the center (Fig. 1).

Methane is expressed by the spatial formula shown in Figure 2, the hydrogen atoms forming a system of satellites

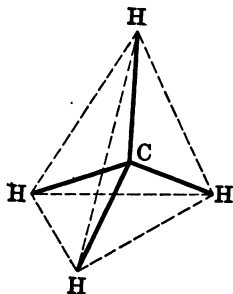


FIG. 2

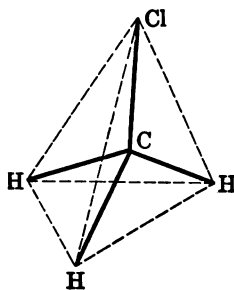


FIG. 3

about the C atom which may be likened to the sun and the planets of the solar system. Chloromethane or methyl chloride is represented by the structure in Figure 3.

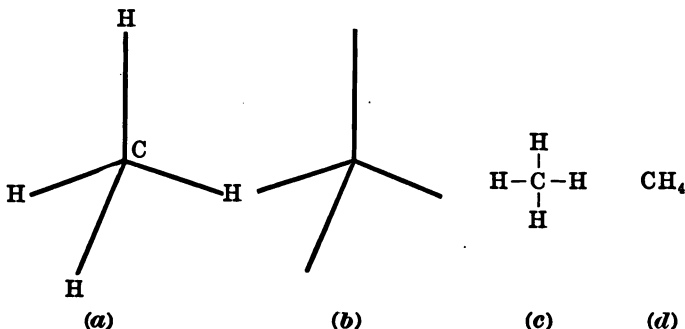


FIG. 4

This formula is, however, so cumbersome to write that in ordinary practice it is not employed. Figure 4 shows the various types of simplified figures employed to describe the carbon atom and its many derivatives produced by the

## 8 Organic Chemistry for Students of Medicine

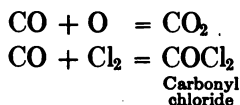
substitution of its hydrogen atoms by other elements or complexes.

Of these symbols  $\text{CH}_4$  is employed in all ordinary cases in writing formulæ. It is known as the *empirical formula*, the geometrical arrangement being employed only for special demonstration. The student should accustom himself to visualize the spatial formulæ.

Now in Figure 2 each of the four hydrogen atoms occupies the same relative position with respect to the C atom and it should make no difference whether, in making chlormethane, we substitute one hydrogen atom, or another, by the chlorine. The methyl chloride should have the same *configuration* in each case, which is equivalent to saying that only one methyl chloride is possible. This is in accord with experience. No matter how methyl chloride be prepared, and there are several methods for its preparation, the product always has the same specific gravity, boiling point, and other physical properties.

In assigning four valences to carbon, it should be borne in mind that there is one very common compound, carbon monoxide,  $\text{CO}$ , in which carbon must exist in the divalent state, or with two of its valences polarized or latent. In a number of its compounds carbon shows a marked tendency to pass from the tetravalent into the divalent state, or vice versa. This is seen in the relation between carbon dioxide and carbon monoxide (also called carbonic oxide). At ordinary temperatures  $\text{CO}_2$  is a stable gas, but under the influence of the silent electrical discharge it tends to change into  $\text{CO} + \text{O}$ . Carbon monoxide on the other

hand can readily add on certain elements, as chlorine, and pass back into the tetravalent state.



The latter reaction takes place very slowly in the dark, but is greatly accelerated by sunlight. Most organic substances exhibit this tendency to pass in some degree into labile active forms.

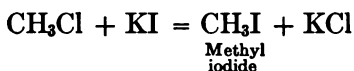
4. If in a mixture of methane and chlorine the latter is present in excess two, three, or four hydrogen atoms are substituted by chlorine. These are called dichlor, trichlor, and tetrachlor methane, respectively. Since the group  $\text{CH}_2$  is termed *methylene* (2), dichlormethane is sometimes called *methylene chloride*. Trichlormethane is *chloroform*, a familiar substance employed as an anesthetic. Tetrachlormethane is familiarly known as *carbon tetrachloride*. It is much employed as a solvent for fats and oils, and is used in the dry cleaning of clothes. Its action is to dissolve the grease from spots and when the latter is removed from the fabric the dirt which adhered to the grease readily separates. Both chloroform and carbon tetrachloride are non-inflammable.

There are bromine and iodine substitution products of methane, entirely analogous to the chlorine compounds. Some of these are of great interest and value in synthetic work. While chlorine reacts with methane at ordinary temperatures, forming substitution products and hydrochloric acid, bromine must be heated in a sealed tube before

## 10 Organic Chemistry for Students of Medicine

any reaction will take place, and iodine will not react with methane, even under pressure and at high temperatures, to form substitution products.

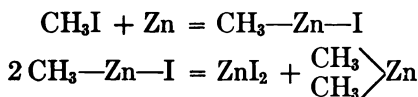
**5. Methyl Iodide.** — For the preparation of the iodine derivatives advantage is taken of the greater affinity of the mono- and divalent metals for chlorine than has the methyl radical, thus :



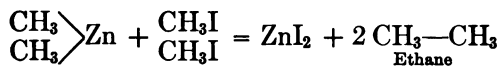
Methyl iodide is a heavy liquid with a pleasant ethereal odor, boiling at 43° C. Its specific gravity is 2.19. It is so unstable that on keeping it decomposes, setting free iodine.

### 6. Ethane, C<sub>2</sub>H<sub>6</sub>.

Zinc methyl:  $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix} \rangle \text{Zn}$  is a derivative of methane which is formed when methyl iodide is warmed with a mixture of zinc and copper in a powdered form. The reaction may be represented as follows :



Zinc methyl is a colorless liquid boiling at 46° C., which is so unstable that it explodes when exposed to the oxygen of the air. It is therefore a highly reactive substance and can be used to build up synthetically other hydrocarbons from methane. Zinc methyl reacts readily with methyl iodide to form *ethane* :



It can also be prepared by the reaction of Wurtz and Fittig, in which methyl iodide is allowed to react with metallic sodium :



Certain metallic derivatives of methane and ethane are of biological importance. Animals poisoned with tellurium or selenium compounds eliminate in the breath dimethyl telluride  $\text{CH}_3\text{—Te—CH}_3$  and dimethyl selenide  $\text{CH}_3\text{—Se—CH}_3$  respectively. These possess characteristic odors, that of dimethyl telluride resembling garlic. The organism is thus capable of employing the methyl radical to combine with these toxic elements in order to produce volatile derivatives which can be eliminated.

Dimethyl telluride is a heavy yellow oil which boils at  $82^\circ$ . Dimethyl selenide is a liquid. When certain molds, especially *Penicillium brevicaulis*, are grown upon media containing arsenic, they produce volatile *diethyl arsine*,  $\begin{matrix} \text{CH}_3\text{—CH}_2 \\ \text{CH}_3\text{—CH}_2 \end{matrix} \rangle \text{AsH}$ , which has a garlic-like odor. The test is so delicate that even 0.00001 gram of arsenic can be detected with certainty.

It is through the agency of such molds that poisoning with arsenic has resulted from the use of wall paper printed with arsenic-containing pigments.

From its method of formation ethane is therefore believed to be made up of a methane molecule in which one hydrogen atom is substituted by a methyl group. Its structure

NOTE. — Unless otherwise specified all temperatures refer to the Centigrade scale.

## 12 Organic Chemistry for Students of Medicine

is assumed to be that shown in Figure 5 (a) and (b), but for simplicity the formulæ (c), (d), or (e) are employed.

Ethane may be regarded as methyl methane and is occasionally spoken of as dimethyl. It is a colorless and odorless gas which is liquefied at  $4^{\circ}$  by 46 atmospheres pressure. It is slightly more soluble than methane in water and alcohol. It occurs with methane in natural gas and is present in petroleum.

The property of the carbon atom of combining with other carbon atoms in a very firm union to form *carbon chains*

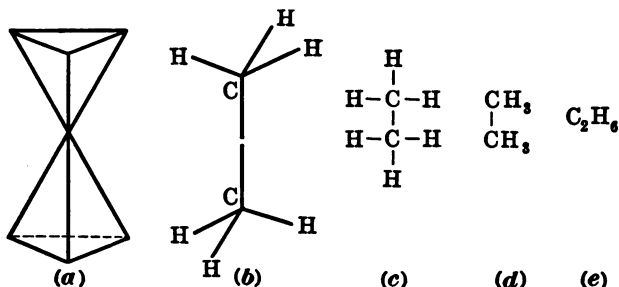
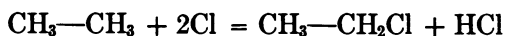


FIG. 5.

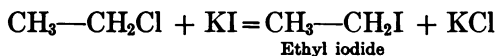
is unique among the elements. Ethane and its *homologues* are very stable substances and very resistant to reagents.

Ethyl chloride,  $\text{CH}_3\text{—CH}_2\text{Cl}$ , can be prepared by the action of chlorine on ethane :

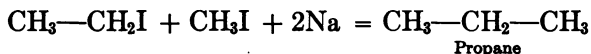


The ethane molecule less one hydrogen atom is called the *ethyl radical* or group. Methyl, ethyl, and their higher homologues are frequently called *alkyl radicals* or groups, and their halogen derivatives *alkyl halides*.

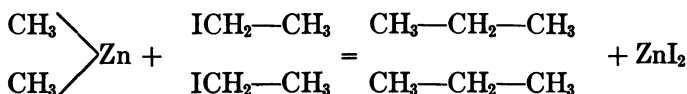
*Ethyl chloride* is a sweet-smelling liquid boiling at 12.5°. In a manner entirely analogous to the formation of methyl iodide, ethyl iodide can be produced from the chloride:



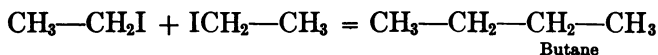
Ethyl iodide boils at 72°. It can react with methyl iodide to produce a hydrocarbon containing three carbon atoms, called *propane*:



This synthesis can also be effected by the action of zinc methyl on ethyl iodide:



If metallic sodium be allowed to act on ethyl iodide, two ethyl radicals are combined to form butane:

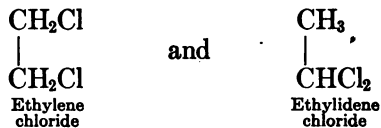


Since it will be necessary later to speak of the dihalogen derivatives of ethane in illustrating the structure of certain compounds (aldehydes), mention should here be made of the nomenclature of these.

When two of the hydrogen atoms of ethane are replaced by halogen, two compounds are possible according to whether the halogen atoms are attached to the same or to different carbon atoms.



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The *symmetrical* isomer is distinguished by the ending *ene* and the unsymmetrical isomer by the ending *idene* preceded by the prefix denoting the hydrocarbon from which it was derived. Compounds of this class will be considered later (31).

7. Starting with methane, therefore, it is possible to build up a series of hydrocarbons each differing from the next lower one by a  $\text{CH}_2$  group. Their formulae,  $\text{CH}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_3\text{H}_8$ ,  $\text{C}_4\text{H}_{10}$ ,  $\text{C}_5\text{H}_{12}$ ,  $\text{C}_6\text{H}_{14}$ , etc., all correspond to the general expression  $\text{C}_n\text{H}_{2n+2}$ . They have the general name of *saturated hydrocarbons*, because all the valences of the carbon atoms not holding other carbon atoms are saturated with hydrogen, so that they cannot take up any more of the latter.

*Nomenclature.* — The saturated hydrocarbons are designated by the termination “ane.” Methane, ethane, propane, and butane, have special names. The higher ones are denoted by the Greek or Latin numeral signifying the number of carbon atoms they contain. Thus,  $\text{C}_6\text{H}_{12}$  is called hexane;  $\text{C}_{10}\text{H}_{22}$ , decane;  $\text{C}_{16}\text{H}_{34}$ , hexadecane; etc.

The groups of atoms which are derived from the hydrocarbons by the removal of a hydrogen atom are termed *alkyl groups*; they are denoted by changing the ending “ane” to “yl.” Thus  $\text{CH}_3\text{—}$ , is methyl;  $\text{C}_2\text{H}_5\text{—}$ , ethyl;  $\text{C}_3\text{H}_7\text{—}$ , propyl;  $\text{C}_4\text{H}_9\text{—}$ , butyl; etc.

*Properties of the paraffins.* The compounds of this series containing from 1 to 4 carbon atoms are gases; those

with 5 to 16 carbon atoms, liquids at ordinary temperatures and pressures; while those having more than 16 carbon atoms in the molecule are solids. Members containing from 1 to 60 carbon atoms are actually known.

8. **Crude Petroleum**, which occurs in nature in enormous quantities, consists of a mixture of all the members of the series from the lowest to the highest. When distilled the lower members volatilize first, the temperature in the still rising as the distillation proceeds. The lightest fraction which is collected distills at  $0^{\circ}$  and consists of gases, chiefly butane, which are liquefied under pressure and employed for the production of cold by evaporation. As a rule the distillate is collected until the product coming over has a specific gravity of .729. This is reached at a temperature of about  $150^{\circ}$ , at which point chiefly nonane and decane distill. All the product so obtained is known as *crude naphtha*. This is redistilled and separated into *rhigolene* B. P.  $18^{\circ}$ , *petroleum ether* or *naphtha* B. P.  $50-60^{\circ}$ , containing chiefly  $C_5H_{12}$  and  $C_6H_{14}$ ; benzine B. P.  $70-90^{\circ}$ , chiefly  $C_6H_{14}$  and  $C_7H_{16}$ ; ligroin B. P.  $90-120^{\circ}$ , and petroleum benzine B. P.  $120-150^{\circ}$ , chiefly mixtures of  $C_7H_{16}$  and  $C_8H_{18}$ . From  $150-300^{\circ}$  there is collected the "burning oil distillate," which is redistilled into several grades of *kerosene*. The safety of these oils depends on their volatility, for their vapors mixed with air form explosive mixtures. Their use is attended with considerable danger. The quality of the product is determined by the *flash point* and "burning point." These are determined by heating a sample in a dish and at intervals bringing a small flame near the surface. When vapors are

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given off rapidly enough to form a combustible mixture, there is a flash, which is at once extinguished. At a higher temperature vapors are given off rapidly enough to support a flame. This is known as the burning point. Most states require a flash point of at least 110° F. and a burning point of 110 to 150° F.

Above 300° F. there are distilled various grades of lubricating oils. From the residues vaseline and paraffin are separated, the latter by chilling.

The physical constants of a number of the normal hydrocarbons are given below :

TABLE I

	MELTING POINT	BOILING POINT	SPECIFIC GRAVITY
CH <sub>4</sub> Methane	- 184°	- 164°	.415 at 16.4°
C <sub>2</sub> H <sub>6</sub> Ethane	- 172.1	- 84.1	.446
C <sub>3</sub> H <sub>8</sub> Propane	- 45	- 44.5	.535
C <sub>4</sub> H <sub>10</sub> Butane	—	- 1	.600
C <sub>5</sub> H <sub>12</sub> Pentane	—	36.3	.454
C <sub>6</sub> H <sub>14</sub> Hexane	—	69	.660
C <sub>7</sub> H <sub>16</sub> Heptane	—	98.3	.683
C <sub>8</sub> H <sub>18</sub> Octane	—	125.8	.702
⋮			
C <sub>16</sub> H <sub>34</sub> Hexadecane	18	287	.775
C <sub>17</sub> H <sub>36</sub> Heptadecane	22	303	.777
C <sub>18</sub> H <sub>38</sub> Octadecane	28	317	.777
⋮			
C <sub>27</sub> H <sub>56</sub> Heptacosane	60	270	.780
C <sub>31</sub> H <sub>64</sub> Hentriacontane	68	302	.781
C <sub>32</sub> H <sub>66</sub> Dotriacontane	70	310	.781
C <sub>35</sub> H <sub>72</sub> Pentatriacontane	75	331	.782

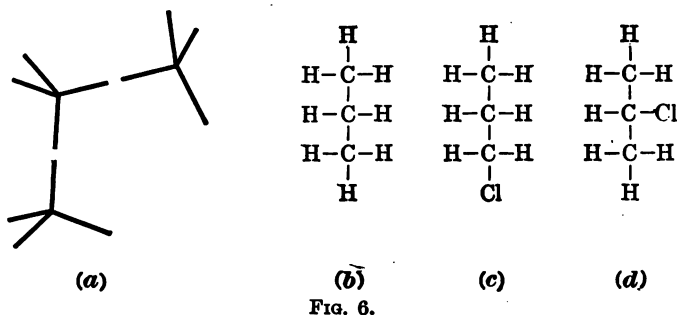
} 40°

} at 20°

} At the  
M. P.

At  
15 mm.  
pressure

**9. Isomerism.** — Just as in the case of methane, there is but one substance known having the formula  $\text{CH}_4$ , so there is but one compound having the formula  $\text{C}_2\text{H}_6$  (ethane), and one having the formula  $\text{C}_3\text{H}_8$  (propane). Butane,  $\text{C}_4\text{H}_{10}$ , however, exists in two forms. They have the same percentage composition with respect to carbon and hydrogen, and the same molecular weight, but differ in their boiling points and specific gravities. Both are



gases, but one is liquefied at  $-1^\circ$  while the other remains a gas until cooled to  $-17^\circ$ . The existence of two or more compounds having the same chemical formula but different physical properties is explained by the structural formulas. Thus while all the hydrogen atoms in methane and ethane are alike with respect to the remainder of the molecule; in propane and butane and the higher homologues this is not the case, as is illustrated in Figure 6.

If in (b) a chlorine atom should be substituted for a hydrogen atom, the same chlor propane or *propyl chloride* should result whichever one of the hydrogen atoms attached to either end carbon atom might be replaced,

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but a different compound should result provided the chlorine should be substituted for a hydrogen attached to the middle carbon atom. This C atom differs from the two end ones in that two of its valences are in union with

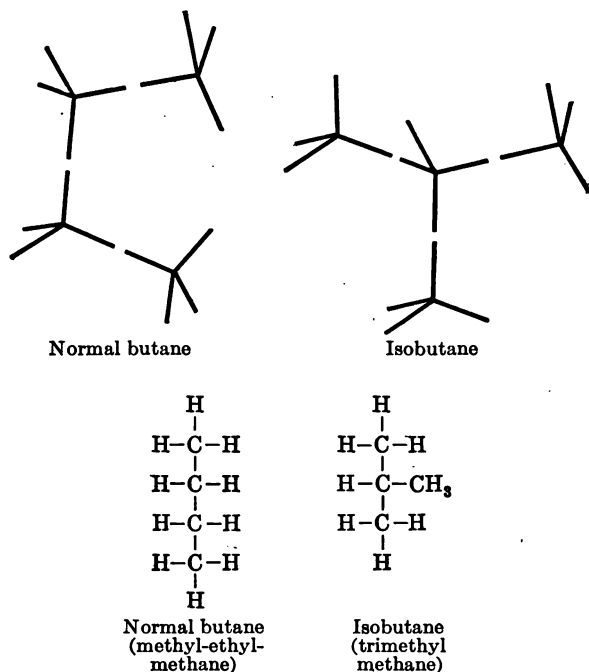


FIG. 7.

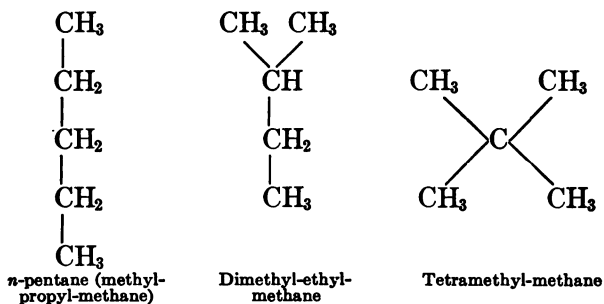
methyl groups, while the others are each linked to carbon by only one bond. Theory calls therefore for only one propane, and only one is known, while it calls for two mono-chlor propanes and both of these are known. *Normal* propyl chloride,  $\text{CH}_3-\text{CH}_2-\text{CH}_2\text{Cl}$ , abbreviated

*n*-propyl chloride, boils at 46.4°, while *isopropyl* chloride,  $\text{CH}_3\text{—CHCl—CH}_3$ , boils at 36.5°.

We should expect in the case of butane two forms corresponding to the propyl chlorides, the methyl group occupying the position of the chlorine atoms (Fig. 7).

Isobutane consists of a *branched chain* of carbon atoms, normal butane does not. Such a difference in structure is called *isomerism* and the compounds so related are *isomers*. Normal butane may be looked upon as methyl-ethyl-methane, since two hydrogens are respectively substituted by a methyl and an ethyl radical.

Three pentanes should exist if our theory of structure is correct and as a matter of fact three are known :

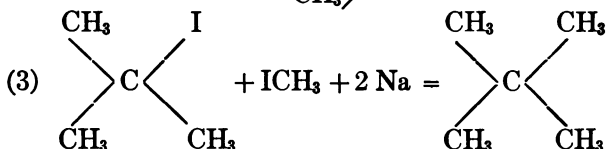
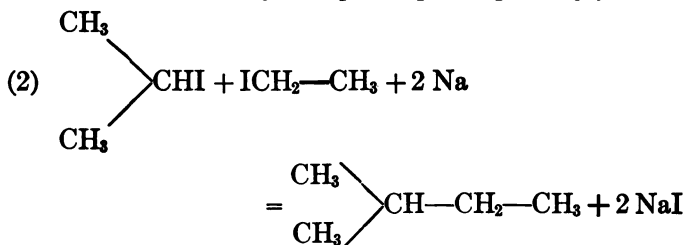
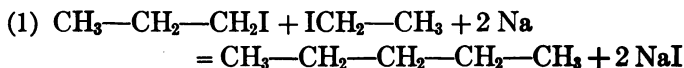


The boiling points of the normal hydrocarbons are always higher than those of the isomers, and the boiling point becomes continuously lowered the more the carbon chain is branched, *i.e.* the more the methyl groups are gathered together in the molecule.

The constitution of the hydrocarbons of the paraffin series can be arrived at only by their synthetical formation

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from simpler ones of known structure. Thus, by the Wurtz reaction one molecule of normal propyl iodide and one of ethyl iodide can yield one molecule of normal pentane (1); one molecule of isopropyl iodide and one of ethyl iodide can yield dimethyl-ethyl-methane (2); and from one of the isobutyl iodides and methyl iodide are obtained tetramethyl methane (3):



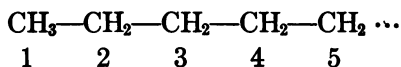
The number of possible isomers increases very rapidly with increasing carbon atoms. The following table shows the number theoretically possible for some of them:

NUMBER OF ISOMERS

Hexane	$\text{C}_6\text{H}_{14}$	5	Decane	$\text{C}_{10}\text{H}_{22}$	75
Heptane	$\text{C}_7\text{H}_{16}$	9	Undecane	$\text{C}_{11}\text{H}_{24}$	159
Octane	$\text{C}_8\text{H}_{18}$	18	Dodecane	$\text{C}_{12}\text{H}_{26}$	354
Nonane	$\text{C}_9\text{H}_{20}$	35	Tridecane	$\text{C}_{13}\text{H}_{28}$	802

Most of these compounds have never been prepared because they are not of sufficient importance to induce chemists to give the necessary effort. The methods of forming them are well understood and it is quite possible to produce large numbers of them synthetically.

10. A carbon atom which is only linked to one other carbon atom is called *primary*; one which is linked to two carbon atoms is *secondary*; one linked to three is *tertiary*; and to four, *quaternary*. When situated at the end of a chain a carbon atom is called *terminal*. The carbon atoms of a chain are designated by numbers, the terminal one being denoted by 1, the next by 2, etc., for example:



Frequently the longer chains are written



The terminal carbon atom is frequently denoted by  $\omega$ , the Greek letter *omega*, the next by  $\alpha$  (*alpha*) and the succeeding ones by  $\beta$ ,  $\gamma$ , etc. Methane and its homologues are collectively spoken of as the *methane series*, or the *paraffin hydrocarbons*.

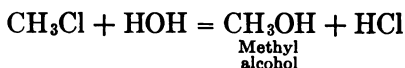
11. The assumption that the four valences of the carbon atom are directed toward the angles of a regular tetrahedron does not necessitate regarding their positions with respect to each other as fixed. There is good reason to believe that they may revolve around a position of equilibrium without changing the order of succession.



## CHAPTER II

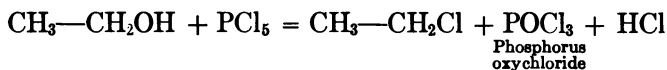
### THE ALCOHOLS

**12. The Monatomic Alcohols.**—When methyl chloride, bromide, or iodide is warmed with water, halogen acid and a new substance, methyl alcohol, are formed. It may be looked upon as water in which one H atom is replaced by the  $\text{CH}_3$  radical.

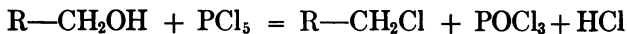


Its synthetic formation has only a scientific interest, for in practice it is always obtained as a by-product of wood distillation.

The alcohols and the corresponding alkyl halides are in general mutually transformable into each other. Thus on treatment with phosphorus pentachloride the alcohols are converted into alkyl chlorides, the OH group being replaced by Cl:



It is customary in illustrating reactions which, like this one, are characteristic of a series by employing the symbol R in place of the alkyl group attached to carbinol, as:



Methyl alcohol is known as wood alcohol because it is produced when wood is heated out of contact with the oxygen of the air to a temperature sufficient to decompose it.

*Properties.* The methyl alcohol of commerce is obtained in this way. It is a colorless liquid which is neutral in reaction; that is, it does not dissociate  $H^+$  or  $OH^-$  ions, a fact which is shown by its failure to act on indicators such as litmus, or to conduct the electric current. It is soluble in water in all proportions, has a burning taste, and boils at  $64.5^\circ$ .

Methyl alcohol is the lowest member of a homologous series of alcohols derived from the hydrocarbons of the methane series, the second member being *ethyl alcohol*  $CH_3-CH_2OH$ .

**13. Nomenclature of the Alcohols.** — Certain of the more common alcohols have received special names which they retain as the result of long usage. In the systematic nomenclature usually employed they are regarded as derivatives of *carbinol* or methyl alcohol. This system is of especial utility in indicating the structures of the isomeric alcohols. Thus ethyl alcohol is *methyl carbinol*,  $CH_3CH_2OH$ , and the two primary butyl alcohols are *propyl carbinol* and *isopropyl carbinol*. Further examples are given in connection with the amyl alcohols (20).

Another system of nomenclature which is frequently employed is that of using the name of the hydrocarbon with the same number of carbon atoms and employing the suffix -ol to indicate the alcohol. Thus methyl alcohol is *methanol*; ethyl alcohol, *ethanol*; etc.

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The relationship of the first five alcohols to the corresponding hydrocarbons is illustrated by the following formulæ :

Methyl alcohol	$\text{CH}_3\text{OH}$	Methanol, carbinol.
Ethyl alcohol	$\text{CH}_3-\text{CH}_2\text{OH}$	Ethanol, methyl carbinol.
Propyl alcohol	$\text{CH}_3-\text{CH}_2-\text{CH}_2\text{OH}$	Propanol, ethyl carbinol.
<i>n</i> -Butyl alcohol	$\text{CH}_3-(\text{CH}_2)_2\text{CH}_2\text{OH}$	Butanol, <i>n</i> -Propyl carbinol.
Isobutyl alcohol	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CH}-\text{CH}_2\text{OH}$	Isobutanol, Isopropyl carbinol.
<i>n</i> -Pentyl alcohol (Amyl alcohol)	$\text{CH}_3-(\text{CH}_2)_3-\text{CH}_2\text{OH}$	<i>n</i> -Pentanol, <i>n</i> -Butyl carbinol.

**14. Ethyl Alcohol, *ethanol*, *methyl carbinol*.**—This is the ordinary alcohol obtained by fermentation of sugar by yeasts. It occurs in all fermented liquids such as wine and beer. It is made chiefly from potatoes, grains, and molasses. The starch is converted into sugar and the latter into alcohol and carbon dioxide. The chemical reactions involved in this process will be described in connection with the fermentation of sugars (164).

Ethyl alcohol is prepared technically by distilling fermented solutions. It is a liquid of agreeable odor, which boils at  $78^\circ$ ; and although the fermented liquids never contain more than 18% of alcohol, by carrying out the distillation in a fractionating column alcohol of 84 to 90% strength may be obtained. The fractionating column is an apparatus in which a relatively large cooling surface is offered and a considerable time is allowed for the condensation of the less volatile liquid. There are

ordinarily placed in the vapors ascending from the still, obstructions such as glass beads or platinum gauze, to retard their escape, thus giving greater opportunity for the condensation of the higher boiling liquid of the mixture, which then runs back into the still. The lower boiling constituent escapes condensation and passes over into the receiver.

On redistilling the alcohol thus obtained in an efficient rectifying apparatus a product containing but 4% of water is obtained. This strength of alcohol is much used in the arts as a solvent.

*Absolute alcohol* is obtained by treating 96 % alcohol with quicklime, which removes the water, forming calcium hydrate,  $\text{Ca(OH)}_2$ . The alcohol is then rectified again. The product so obtained contains about .5 % of water. This is the commercial absolute alcohol. Pure absolute alcohol is obtained by treating the latter with a small amount of metallic sodium or calcium and distilling again. Traces of water in alcohol can be readily detected by placing in it a small amount of copper sulphate from which the water of crystallization has been driven off by heating. This is a white powder. The anhydrous  $\text{CuSO}_4$  takes up even very slight traces of water from the alcohol and forms the deep blue hydrated salt.

Among inorganic substances alcohol dissolves the halogens, sulphur and phosphorus to some extent, boracic acid, the hydrates of potassium and sodium, the chlorides of calcium and strontium, ferric chloride and mercuric chloride. It is also a solvent for many organic acids, bases, and neutral substances, the resins, soaps, and fats. Alco-

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holic solutions of substances employed in medicine are called essences, spirits, and tinctures. Certain proteins of the cereal grains readily dissolve in 70 % alcohol, but most proteins are precipitated from their solutions by alcohol.

For use in the arts alcohol is now sold without the payment of the internal revenue tax which is levied on all alcoholic beverages. Such alcohol to be tax free must be *denatured* or rendered unfit for drinking by the addition of poisonous and distasteful substances. The regulations of the United States Commissioner of Internal Revenue prescribe the addition of 10 parts of methyl alcohol and 1 part of benzine to each 100 parts of alcohol. Another formula which may be used requires the addition of 2 parts of wood alcohol and 1 or 2 parts of pyridine.

Ethyl alcohol is widely distributed in nature. Small amounts of it are found in the distillate from leaves, flowers, in the ethereal oils, and in humus-rich soil. Traces occur in bread made with yeast. Very small amounts are regularly found in the blood and tissues of animals. Indeed there are strong reasons for believing that in the destruction of sugar through the normal physiological processes, ethyl alcohol is an intermediate product.

**15. The Alcoholates.** — Metallic sodium reacts with great energy on alcohol, forming sodium ethylate and hydrogen:



Sodium ethylate is readily soluble in alcohol and forms a crystalline compound  $\text{C}_2\text{H}_5\text{ONa} + 2\text{C}_2\text{H}_5\text{OH}$ . This loses its alcohol at 200°, leaving the sodium ethylate as a white powder. It is very useful in synthetic work.

Potassium acts violently on alcohol, forming potassium ethylate.

**16. Alcoholic Beverages.** — There are two classes of alcoholic beverages in use: those which are the direct product of fermentation by yeast; and those which are prepared by distilling the fermented liquid, as molasses or extracts, prepared by conversion of the starches of certain grains, potatoes, etc., into sugar, and dissolving out the latter. The undistilled beverages contain much less alcohol than the distilled.

*Beer* is prepared by fermenting malted (*i.e.* sprouted) grains. It contains 3 to 5 per cent of alcohol and derives its bitter taste from the addition of an infusion of hops.

*Wine* and *champagne* are fermented fruit juices, principally grape juice. As fermented, a beverage never contains more than about 15 to 18 per cent of alcohol, but wines are frequently "fortified" by the addition of alcohol to a content of 20 %.

*Whiskey* is prepared by the fermentation of malted grains. After the fermentation by yeast is completed, the product is distilled and the distillate condensed. Ordinarily it is twice distilled and water is added to the distillate to make a solution containing about 50 to 58 % of alcohol by volume.

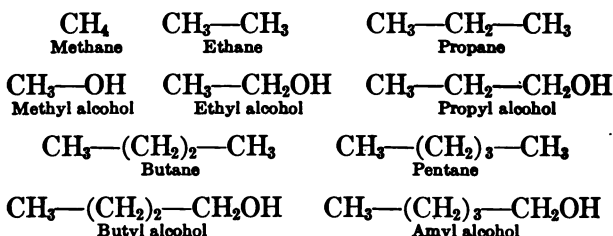
*Brandy* is made by distilling wines or fermented peach, apple, or other juices. Its alcohol content varies from 44 to 55 %.

*Gin* is whiskey which has been distilled with aromatic substances such as juniper berries, anise seed, etc., which give it its peculiar flavor.

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*Rum* is made from fermented molasses. It not infrequently contains enough of the higher alcohols, butyl and amyl alcohols and their esters, to render it more toxic than ordinary whiskey prepared from grains.

### 17. Higher Homologues of Ethyl Alcohol. —



Being derived from the hydrocarbons of the  $\text{C}_n\text{H}_{2n+2}$  series by the replacement of H by OH these alcohols have the general formula  $\text{C}_n\text{H}_{2n+1}\text{OH}$ . Those derived from the normal hydrocarbons are normal alcohols. If the OH group is attached to an end carbon atom it is known as a *primary*; if to a secondary carbon atom, a *secondary*; and if to a tertiary carbon atom, a *tertiary* alcohol. Those derived from branched chain hydrocarbons are *iso* alcohols, and may be primary or secondary :



### 18. The Butyl Alcohols. — $\text{C}_4\text{H}_9\text{OH}$ .

	BOILING POINT	SPECIFIC GRAVITY AT 20°
1. $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{OH}$ Normal butyl alcohol (primary) (Propyl carbinol)	117°	.810



Isobutyl alcohol (primary)  
(Isopropyl carbinol)



Normal secondary butyl alcohol  
(Methyl ethyl carbinol)



Tertiary butyl alcohol  
(Trimethyl carbinol)

Normal primary butyl alcohol occurs in fusel oil to a small extent, but has little biological importance. It is produced, together with a number of other products, by *Bacillus butylicus*, growing on glycerin and various sugars and related substances (see butyric acid fermentation, 164).

The most important butyl alcohol is *isopropyl* carbinol. It is produced by yeasts during fermentation of sugar into ethyl alcohol and carbon dioxide. It has its origin not from sugar, but from one of the protein digestion products, valin. It is formed in relatively large amounts when potatoes are malted and fermented by yeasts, because the mother substance valin (73) is present in greater amount than in the malted grains.



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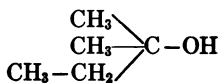
The remaining two butyl alcohols have been prepared synthetically, but do not occur in nature.

*Physiological properties.* — The butyl alcohols are all distinctly poisonous both to plants and animals. The toxic action of monatomic alcohols increases with higher carbon content and with increasing molecular weight. This is the *Rule of Richardson*. The normal primary alcohol is more toxic than isopropyl carbinol, and the latter is more toxic than secondary and tertiary butyl alcohols.

#### 19. The Amyl Alcohols. —

		BOILING POINT	SPECIFIC GRAVITY AT 20°
1. Normal primary (butyl carbinol)	$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{OH}$	138°	.817
2. Isobutyl carbinol (primary) (Active amyl alcohol)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>CH}-\text{CH}_2-\text{CH}_2\text{OH}$	130°	.810
3. Secondary butyl carbinol (primary)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3-\text{CH}_2 \end{array} \text{>CH}-\text{CH}_2-\text{CH}_2\text{OH}$	128°	.816
4. Tertiary butyl carbinol (primary)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>C}-\text{CH}_2\text{OH}$	113°	—
5. Methyl propyl carbinol (secondary)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3-\text{CH}_2-\text{CH}_2 \end{array} \text{>CHOH}$	119°	—
6. Methyl isopropyl carbinol (second- ary)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>CH}-\begin{array}{c} \text{CH}_3 \\ \text{CHOH} \end{array}$	112°	.819
7. Diethyl carbinol	$\begin{array}{c} \text{CH}_3-\text{CH}_2 \\ \text{CH}_3-\text{CH}_2 \end{array} \text{>CHOH}$	117°	—

8. Dimethyl ethyl  
carbinol (tertiary)



102° —

The only two amyl alcohols which are of any great importance in biological processes are *primary isobutyl carbinol* and *secondary butyl carbinol*. These both occur in fusel oil through the life processes of yeasts, and, like isobutyl alcohol, are derived from the cleavage products of proteins (75).

*Physiological Properties.* — All have disagreeable smells and produce headache. Normal amyl alcohol is about four times as toxic as ethyl alcohol. A .5 % solution quickly destroys infusoria, and a 1 % solution kills algæ within a day. In dilutions as great as .1 % certain bacteria can use it as a source of carbon.

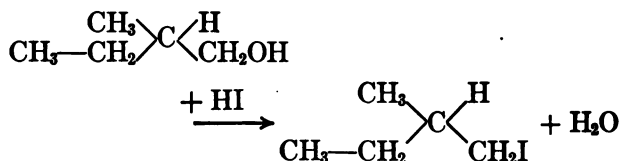
A saturated (2.5 %) solution of isoamyl alcohol exerts a powerful bactericidal action. The toxicity of the amyl alcohols is distinctly greater than that of the lower members of the series. A  $\frac{1}{10}$  n solution is as destructive to *B. pyogenes* as a  $\frac{3}{10}$  n solution of butyl, a  $\frac{5}{10}$  n solution of propyl, a  $1\frac{3}{10}$  n solution of ethyl, and a  $2\frac{1}{2}$  n solution of methyl alcohol.

**20. Isomerism of the Amyl Alcohols.** — One of the amyl alcohols, secondary butyl carbinol, also called active or fermentation amyl alcohol, presents a very interesting case of isomerism. Three isomers of this one alcohol are known, but they have all the same chemical and, with a single exception, the same physical properties. This exception is found in their action on polarized light. The ray of polarized light may be likened to a ribbon of light, as contrasted with a ray of ordinary light the waves of which are vibrating in every direction at right angles to the path

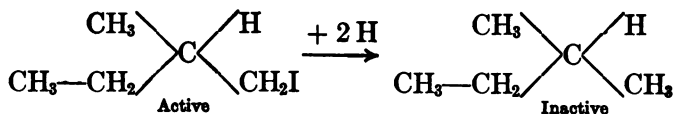
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of the ray. In the polarized ray the vibrations all lie in the same plane. When such a ray is passed into either of two of these amyl alcohols the ray is rotated by one of them to the right and by the other to the left. One is said to be dextrorotatory, the other levorotatory. The third produces no rotation at all. Two are said to be *optically active*; the other, *inactive*. The effect is as if the ray had received a twist in passing through the optically active substance.

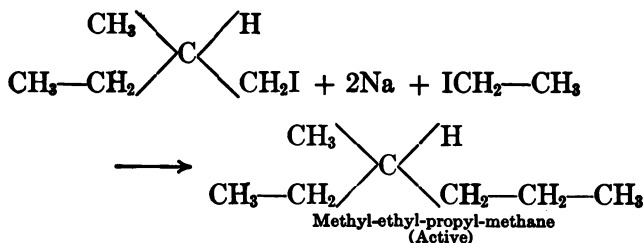
Now these two active isomers when treated with gaseous HI are transformed into two optically active amyl iodides, and the inactive one into an amyl iodide which is not optically active.



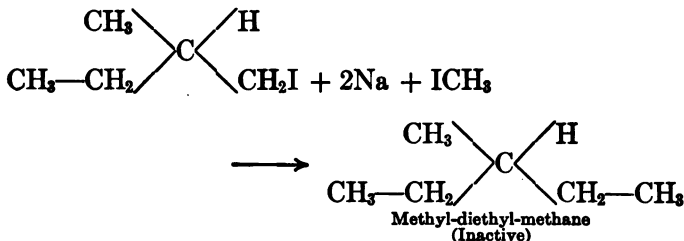
The amyl iodides, like the alcohols from which they were derived, have identical chemical and, except in their behavior toward polarized light, the same physical properties. Suppose we consider the iodide which is derived from *levorotatory amyl alcohol*, which is the important one from the biological standpoint. If it be converted into *pentane* by the action of nascent hydrogen, which removes the iodine, replacing it by H, there results a pentane which is *optically inactive*:



On the other hand, if this iodide is caused to react with ethyl iodide in the presence of sodium, there is produced a *heptane* which is optically active :



If the above reaction is carried out with methyl iodide instead of ethyl iodide there is formed a *hexane* which is optically inactive :



An inspection of these formulas shows that those compounds are optically active in which each of the bonds of affinity of one carbon atom is linked to different groups or atoms. Whenever two bonds of this carbon atom are linked to the same kind of group (as two methyl or two ethyl groups) the optical activity is lost.

Van't Hoff first discovered that optically active compounds have in general at least one carbon atom which is

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linked to four different atoms or radicals. He gave the name "asymmetric" carbon atom to one so linked.

Van't Hoff further showed that the existence of three isomers must necessarily result from the structure of an asymmetric carbon atom, if the assumption be correct that the four valences of the carbon atom are directed as toward the four solid angles of a regular tetrahedron, the carbon atom itself occupying the center of the figure.

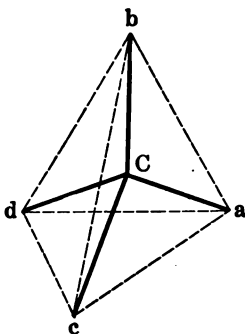


FIG. 8.

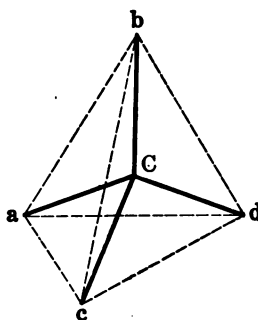
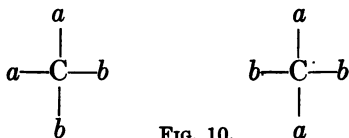


FIG. 9.

With such an arrangement there must result two kinds of molecules which resemble each other in the same way as the right hand resembles the left, or as an object resembles its reflection in a mirror. If such molecules be represented as mirror images (Fig. 8 and Fig. 9) it will be seen that on turning one so that the *a* and *b* in both figures coincide, the *c* and *d* of one will not coincide with *c* and *d* of the other. If now Figure 8 rotates the plane of polarized light to the right, Figure 9 will rotate it to the left because of its opposite handed structure. This isomerism in space is termed *stereochemical isomerism* or *stereoisomerism*.

For simplicity the formulæ of asymmetric compounds are written as if all the atoms or groups lie in the same plane. The belief that the atoms and groups in the compounds under discussion do not lie in the same plane is supported by the fact that compounds containing but two dissimilar groups, as  $C aabb$ , do not exist in two isomeric forms. If all were in the same plane two arrangements, like Figure 10, would be possible, which must lead to different physical properties because in the one case like groups are separated by unlike ones, while in the other like groups are adjacent to one another. No isomers of this type have ever been observed, although there are known a large number of compounds of the general formula  $Ca_2b_2$ .



The third isomer of this amyl alcohol is a mixture of equal numbers of molecules of the right- and left-handed varieties. The influence of one-half of the molecules in rotating the plane of polarized light in one direction is exactly counteracted by the opposite rotating power of the other half, with the result that it appears to be without optical activity. When an excess of one optical form exists in a mixture of the two optically active varieties, this part exerts its effect and the mixture becomes optically active in proportion to the excess of one variety over the other.

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This type of isomerism is of great significance in biology, since with but few exceptions the organic compounds which play important rôles in the life processes of plants and animals possess this type of asymmetry.

**21. The Higher Alcohols.** — One of the higher homologues of methyl alcohol which should be mentioned, is normal *hexyl* alcohol,  $\text{CH}_3-(\text{CH}_2)_4-\text{CH}_2\text{OH}$  (B. P.  $157^\circ$ ) which occurs in the oil of the seeds of *Heracleum giganteum*, in the oil of the fruit of several plants, and in slight amount in fusel oil. The following are also biologically important:

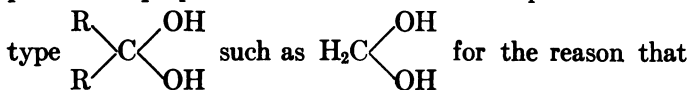
Normal heptyl alcohol	$\text{CH}_3-(\text{CH}_2)_5-\text{CH}_2\text{OH}$	B. P. $176^\circ$
Normal octyl alcohol	$\text{CH}_3-(\text{CH}_2)_6-\text{CH}_2\text{OH}$	B. P. $196^\circ$
Nonyl alcohol	$\text{CH}_3-(\text{CH}_2)_7-\text{CH}_2\text{OH}$	B. P. $213^\circ$
Dodecyl alcohol	$\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2\text{OH}$	M. P. $24-26^\circ$
Cetyl alcohol	$\text{CH}_3-(\text{CH}_2)_{14}-\text{CH}_2\text{OH}$	M. P. $49^\circ$
Octadecyl alcohol	$\text{CH}_3-(\text{CH}_2)_{16}-\text{CH}_2\text{OH}$	M. P. $59^\circ$
Carnaubyl alcohol	$\text{CH}_3-(\text{CH}_2)_{22}-\text{CH}_2\text{OH}$	M. P. $68^\circ$
Ceryl alcohol	$\text{C}_{26}\text{H}_{53}\text{OH}$	
Myricyl alcohol	$\text{C}_{30}\text{H}_{61}\text{OH}$	

The higher alcohols,  $\text{C}_8$  to  $\text{C}_{18}$ , are found in various plant oils in small amounts usually combined with organic acids, as esters (28). Cetyl alcohol occurs as a constituent of spermaceti, an animal wax derived from the sperm whale, and in the oil secreted by water birds for lubricating their feathers.

Ceryl alcohol is an important constituent of many waxes, as Chinese wax, beeswax, etc.

Myricyl alcohol is likewise a very common constituent of waxes. (See waxes, 95.)

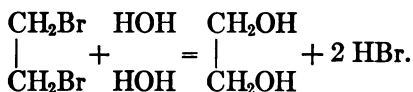
**22. The Diatomic Alcohols.** — It has been found impossible to prepare in the isolated state compounds of the



they are unstable and as soon as formed they separate a molecule of water with the formation of a new class of compounds, the aldehydes. These will be treated more fully later (30).

There are, however, many examples of compounds which contain more than one alcohol radical. The simplest of these is *ethylene glycol* or *glycol*  $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$ . It is formed

in a manner analogous to monatomic alcohols, viz., by the action of water or metallic hydroxides on ethylene halogen derivatives (6). Ethylene chloride is too stable to react with water directly even under pressure, but ethylene bromide will react when heated in a sealed tube with water, forming glycol and hydrobromic acid :



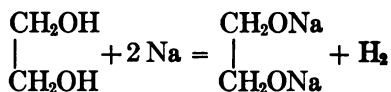
Glycol is a colorless liquid, readily soluble in water, and has a sweet taste. It boils without decomposition at 197° and solidifies in a freezing mixture. Its melting point is -11.5° and its specific gravity at 0° is 1.125, water being 1.000. It is therefore heavier, volume for volume, than any of the monatomic alcohols, which are all lighter than water.



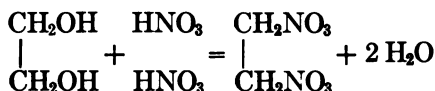
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Glycol does not occur in nature in the free state, but is a constituent of a very important class of compounds of complex structure, the lecithins (96). Moreover it is of great theoretical interest, since it probably occurs as an intermediary product in the degradation of certain food-stuffs in the processes of metabolism (48).

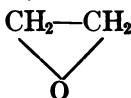
Glycol reacts with alkali metals, as do the monatomic alcohols, forming *e.g.* sodium, or potassium glycollate, and hydrogen:



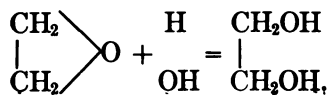
With fuming nitric acid it reacts to form glycol dinitrate:



*Glycol chlorhydrin*,  $\text{CH}_2\text{OH}-\text{CH}_2\text{Cl}$ , is obtained by passing hydrochloric acid gas into warm glycol (25). It is a liquid, soluble in water, and boiling at  $130^\circ$ .

23. Ethylene Oxide. — . Glycol does not

form an *anhydride* on treating it with reagents which abstract water. From glycol chlorhydrin, by abstracting a molecule of HCl by treatment with alkalis, there results ethylene oxide. This compound is a gas, since it boils at  $14^\circ$ . It readily takes up water, forming glycol:

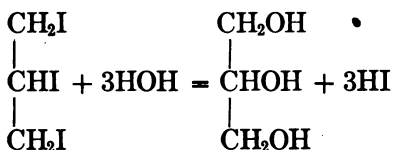


It also readily adds hydrochloric acid, forming glycol chlorhydrin:

$$\begin{array}{c} \text{CH}_2 \\ | \\ \text{CH}_2 \end{array} \text{O} + \begin{array}{c} \text{H} \\ | \\ \text{Cl} \end{array} = \begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CH}_2\text{Cl} \end{array}$$

24. From propane two glycols are derived: *Alpha* or  $\alpha$ -propylene glycol  $\text{CH}_3 - \text{CHOH} - \text{CH}_2\text{OH}$ , in which one hydroxyl group is attached to the middle carbon atom and therefore in the *alpha* position to the end carbon atoms, and *Beta* or  $\beta$ -propylene glycol, in which each hydroxyl is bound to an end carbon atom and is therefore in the  $\beta$ -position to the other.

25. **Triatomic Alcohols.** — Glycerol, commonly called glycerine, a name which it received before the modern system of chemical nomenclature was developed, is a derivative of propane, from which it is formed by the substitution of three hydroxyl groups for three hydrogen atoms. It is a never-failing constituent of all fats, where it occurs in combination with the fatty acids. It has been prepared synthetically from triiodo-propane by the action of water:

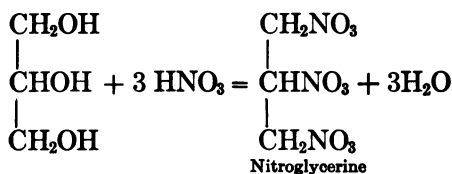


Glycerol reacts with phosphorus triiodide,  $\text{PI}_3$ , to form the triiodo propane, this being also called triiodo-hydrin.

Glycerol is a colorless, odorless, oily liquid of sweet taste. It has a strong affinity for water, and takes up moisture from the air. It is soluble in water and in alcohol in all proportions, but very nearly insoluble in ether. On

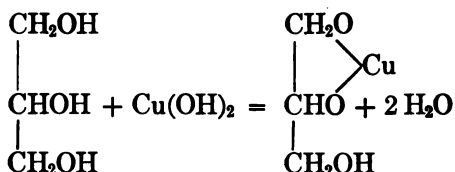
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long standing at low temperatures it solidifies, and the crystals thus formed do not melt below 17°. It boils at 290° but undergoes some decomposition. Under reduced pressure it can be distilled without decomposition. At 12 mm. it distills at 170°. It is slowly volatile with water vapor. Its specific gravity at 15° is 1.265. Its chemical behavior is in accord with the theory that it is a triatomic alcohol. Thus when glycerol is slowly dropped into a mixture of concentrated sulphuric acid and fuming nitric acid trinitroglycerol, usually called *nitroglycerine*, is formed. The sulphuric acid facilitates the reaction by its affinity for water, which it withdraws from the system as soon as formed :



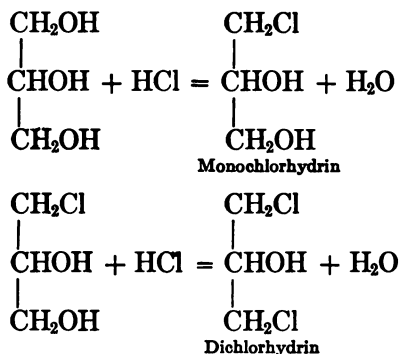
Nitroglycerine is a heavy colorless oil when pure, but usually has a yellow color. It is sweet to the taste and is extremely poisonous, acting chiefly on the central nervous system. It is employed in medicine for its action on the heart and is directly injected into the blood as a remedy in case of carbon monoxide poisoning. When heated to 180° it explodes. Its explosion can be induced by a sharp blow. The principal use of nitroglycerine is as an explosive. When absorbed by certain porous substances, as sawdust, clay, wood pulp, etc., it forms dynamite. Mixed with nitrocellulose, vaseline, and acetone, it forms the smokeless powder called *cordite*.

Glycerol, like other compounds containing several hydroxyl groups, dissolves alkalies and oxides of the heavy metals, forming compounds analogous to the alcoholates. The hydrogen atoms of the OH groups are in these replaced by the metal. The structure of such compounds may be illustrated by the following formula :



With basic lead acetate and ammonia glycerol forms an insoluble lead glycerate.

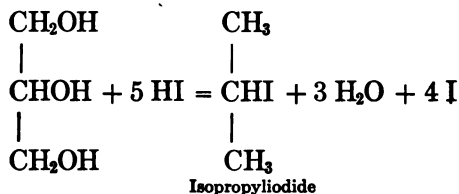
When heated with hydrochloric acid, glycerol reacts with the formation of water and the replacement of one or two hydroxyl groups by chlorine :



This reaction cannot be effected by the use of hydriodic acid, since the latter acts as a strong reducing agent, owing

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to the great tendency it shows to separate free iodine, thus making available nascent hydrogen for the abstraction of oxygen. Thus on heating glycerol with five molecular equivalents of hydriodic acid, isopropyl iodide is produced :



Under carefully regulated conditions this reaction is nearly quantitative, and on the measurement of the iodine in the isopropyl iodide produced from a sample depends the quantitative estimation of glycerol proposed by Zeisel and Fanto.

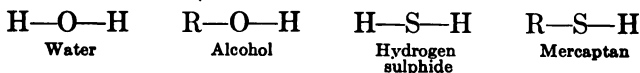
Glycerol is readily oxidized, *i.e.* it exerts a reducing action (abstraction of oxygen) on Fehling's solution even in the cold, owing to its conversion into glyceraldehyde (36).

### 26. Erythritol or Erythrite,

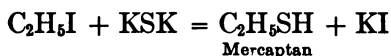


exists in nature in certain algæ.

**27. The Sulphur Alcohols. Mercaptans.** — Just as the alcohols are derivatives of water, formed by replacing one of the hydrogen atoms by an alkyl group, so also there exists a class of compounds of analogous constitution derived from hydrogen sulphide. These are known as *thio-alcohols*, *mercaptans*, or alkyl sulph-hydrates :



They are formed by warming alkyl halides with potassium sulph-hydrate in concentrated aqueous or alcoholic solution :



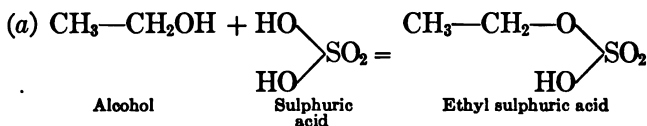
*Methyl mercaptan*,  $\text{CH}_3\text{SH}$ , is a gas, B. P.  $6^\circ$ . It is produced by the action of anaërobic bacteria on proteins, being one of the products of putrefaction. It has a disgusting odor. It is a constituent of intestinal gases.

*Ethyl mercaptan*,  $\text{CH}_3\text{—CH}_2\text{SH}$ , is a liquid with an extremely obnoxious odor ; B. P.  $36^\circ$ . It reacts with sodium, forming  $\text{C}_2\text{H}_5\text{SNa}$ , analogous to sodium alcoholate.

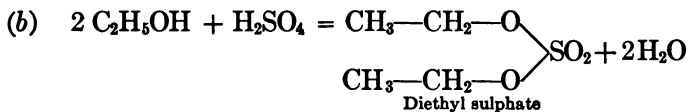
## CHAPTER III

### ESTERS AND ETHERS

**28. Esters.** — When alcohols are treated with acids which have a strong affinity for water, a reaction may take place in which a molecule of water and a new compound called an *ester* are produced. Thus the action of hydriodic acid on alcohol with the production of an alkyl halide (20) is representative of a general type of reaction. Thus:

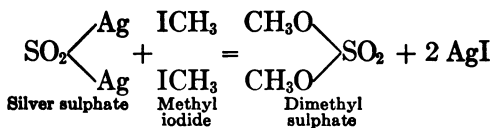


Compounds of the type of ethyl sulphuric acid are known as *ethereal acids*.



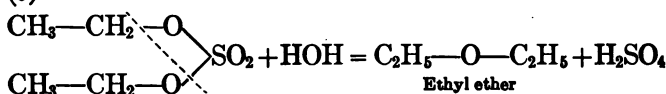
Diethyl sulphate is a neutral ester.

These compounds can also be formed by the action of the silver salts of the acids on the alkyl iodides:

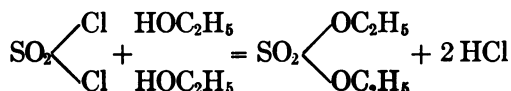


Diethyl sulphate is a colorless oily liquid possessing a peppermint odor. It is insoluble in water. It boils at  $208^{\circ}$ . It is readily hydrolysed, *i.e.* broken up with the entrance of water into the compound, but the original substances, alcohol and sulphuric acid, from which it was formed, are not regenerated. Instead diethyl ether is produced (29).

(c)



The structure of diethyl sulphate is also shown by its formation from alcohol and sulphuryl chloride,  $\text{SO}_2\text{Cl}_2$ .



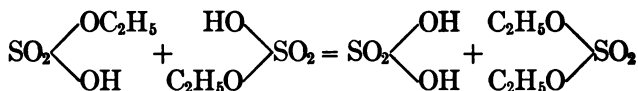
(d) **Ethyl Sulphuric Acid** is a strongly acid liquid of an oily character and possesses no odor. It is soluble in water in all proportions. It is obtained by mixing alcohol with strong sulphuric acid. The calcium and barium salts are soluble while barium sulphate is insoluble. The solution containing ethyl sulphuric acid, alcohol, and sulphuric acid is neutralized with  $\text{BaCO}_3$  and the  $\text{BaSO}_4$  filtered off. On adding just enough sulphuric acid to combine with the barium in the filtrate the barium is removed and free ethyl sulphuric acid is left in solution. It is not very stable, decomposing slowly into alcohol and sulphuric acid in the presence of water at ordinary temperatures and quickly on boiling. Potassium ethyl



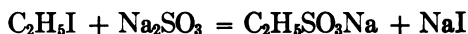
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sulphate is very stable and can be recrystallized from boiling alcohol.

When ethyl sulphuric acid is heated it forms the neutral ester diethyl sulphate and free sulphuric acid :

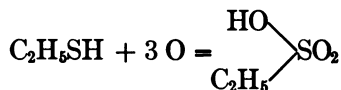


(e) **Esters of Sulphurous Acid.** — When alkyl iodides react with sodium sulphite there is formed the sodium salt of ethyl sulphonic acid :



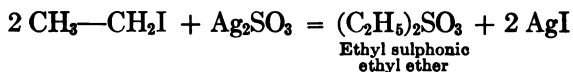
The free acid  $\text{C}_2\text{H}_5\text{SO}_3\text{H}$  is a very stable strong monobasic acid easily soluble in water. It is not saponified even by boiling with water or alkalies. Even boiling concentrated nitric acid does not act upon it, nor does free chlorine, but fused potassium hydroxide decomposes it, regenerating alcohol and forming potassium sulphite.

The same compound is formed by the oxidation of mercaptan with nitric acid or potassium permanganate :



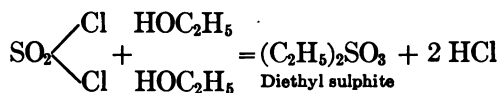
That this acid contains a hydroxyl group is shown by its yielding with  $\text{PCl}_5$  an acid chloride which decomposes with water, regenerating the acid. The method of formation also shows that the sulphur is linked directly to carbon.

By the action of alkyl iodide on silver sulphite sulphonic ethers are formed.



This is so stable that it is difficultly saponifiable. B. P. 213°.

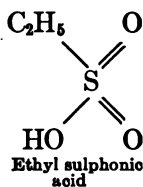
(f) **Ethers of Sulphurous Acid.** — When alcohol reacts with sulphuryl chloride there is formed a compound which is isomeric with ethyl sulphonie ethyl ether, but has entirely different properties :



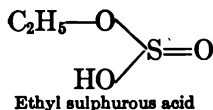
Diethyl sulphite is rapidly saponified by water. On careful partial saponification the unstable potassium salt.

of ethyl sulphurous acid  $\begin{array}{l} \text{C}_2\text{H}_5 \\ \text{H} \end{array} \text{SO}_3$  is formed. The free

acid which is isomeric with ethyl sulphonie acid is incapable of existence, decomposing at once into its components. The stable ethyl sulphonie acid, being known to have its sulphur directly linked to carbon and to contain one hydroxyl group, is assigned the structure :



and the isomeric ethyl sulphurous acid the following :



(g) Ethyl alcohol reacts with nitric acid  $\text{HONO}_2$  to produce ethyl nitrate :



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remains behind in the still. This tends therefore to cause a progressive decrease in the amount of ethyl sulphuric acid in the flask, so that after a time little or no ether is formed. Instead the alcohol distills over as fast as added. The latter is removed from the distillate by neutralizing the  $\text{H}_2\text{SO}_4$  with milk of lime. The alcohol passes principally into the water layer, and the ether, which is separated from the water layer in a separatory funnel, is again distilled.

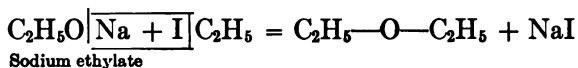
The last traces of water and alcohol are removed from ether by placing in it granulated calcium chloride, which has a strong affinity for both these substances.

Ethyl ether boils at  $34.97^\circ$ . It has an agreeable odor. Prolonged breathing of it causes loss of consciousness. It is much employed in surgery as an anæsthetic. One volume dissolves in 11.1 volumes of water at  $25^\circ$ , and ether dissolves water to the extent of about a 2% solution by volume at  $12^\circ$ . It is much less soluble in a saturated salt solution. With air ether vapors produce highly explosive mixtures. Great care should be exercised therefore in handling ether wherever there is a possibility of ignition, as during distillation. It is best to place the distillation flask in hot water and to dispense with a flame. A small flask should be employed and fresh portions of ether added from time to time, as the distillation proceeds. Small receivers frequently emptied are preferable to one large one.

Ether dissolves a great variety of chemical substances and is indispensable as a solvent in chemical work. In many instances substances can be separated from complex

mixtures by extracting a water solution with ether. This depends upon the fact that when a substance is soluble in two liquids which do not mix, as ether and water, it will, when water and ether are shaken together and then allowed to separate into two layers, distribute itself between the ether and the water. If now the ether be separated from the water by means of a separatory funnel, and fresh ether shaken with the water, a division of the dissolved substance will again take place. In this manner by shaking repeatedly with fresh portions of ether the water solution becomes progressively poorer in the dissolved substance. The ether on evaporation leaves behind the material which it contained.

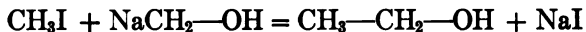
The constitution of the ethers is further shown by their formation from an alcoholate and an alkyl halide:



This reaction serves to show what actually happens when sodium reacts with an alcohol (15). There are two possibilities. The sodium might replace one of the hydrogen atoms which is linked with carbon, or that one which is linked to oxygen. If the former were true, we should have formed a compound of the following structure:



On causing this to react with an alkyl iodide there should be formed a *higher alcohol*:



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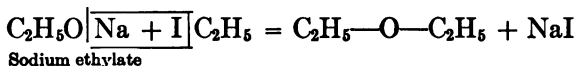
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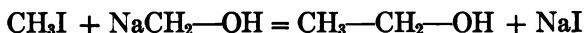
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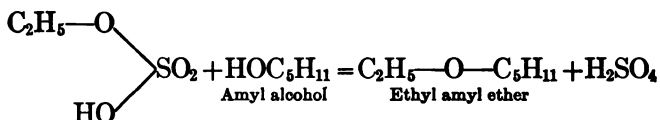
On causing this to react with an alkyl iodide there should be formed a *higher alcohol*:



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The formation of ethers in this way proves that in these the two alkyl groups are linked together through oxygen. This is called Williamson's reaction, after the name of its discoverer.

If to the mixture of alcohol and sulphuric acid (containing ethyl sulphuric acid) there is added, beginning just before distillation commences, an alcohol other than ethyl alcohol, a *mixed* ether will result. In this way numerous ethers containing different alkyl radicals can be produced.



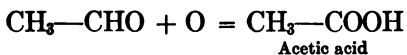
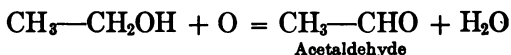
This furnishes further evidence that the steps in the formation of ether are as described above.

## CHAPTER IV

### THE ALDEHYDES AND KETONES

**30. Oxidation Products of the Alcohols.** — It has long been known that alcohol-containing solutions, as fermented cider, wine, or beer, soon become sour when exposed to the air in open vessels at room temperature. *Vinegar* is formed through the change of alcohol into *acetic acid*. In the absence of oxygen this change does not take place, and it is greatly accelerated by thorough aëration of the solution, as by causing it to pass through porous material. The oxidation is not spontaneous, but results from the growth in the solutions of a microörganism *Mycoderma aceti*, or “mother of vinegar.” If the vessel containing the alcoholic solution which is undergoing this change admits but an inadequate supply of air (oxygen) there accumulates an intermediary product known as *aldehyde* or, from its relation to acetic acid, *acetaldehyde*.

The change which takes place in these processes is shown by the following equations:



Oxygen of the air (molecular oxygen) cannot effect this oxidation, except through the agency of an “oxygen carrier,” or catalyzer, which “activates” it. This action

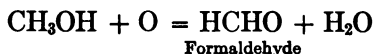


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is brought about by the presence in the acetic acid organism of *oxydases*.

Numerous examples are known of the activation of molecular oxygen through the agency of inorganic catalyzers. Thus a mixture of hydrogen and air is stable at ordinary temperatures and can be left for a long period without the hydrogen and oxygen combining to form water. If a platinum spiral be introduced into such a mixture, the volume of the gas mixture will decrease noticeably and the platinum grow warm. The hydrogen and oxygen will now rapidly combine. If instead of a platinum spiral very finely divided metal, platinum sponge, be employed, the two elements may combine with explosive violence.

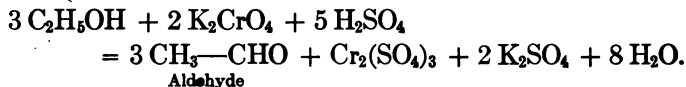
Another example of the effect of an inorganic catalyzer is seen in the technical process of converting methyl alcohol into formaldehyde. Air and methyl alcohol in the proper proportions to supply oxygen for the oxidation of the alcohol form a relatively stable mixture. It can be heated to a relatively high temperature without any oxidation taking place. If however a copper gauze which has been oxidized on its surface be warmed gently and the air-alcohol mixture passed slowly over it, the oxidation of the alcohol is rapidly effected, water and formaldehyde being formed. The heat generated by the oxidation serves to keep the copper in a glowing condition :



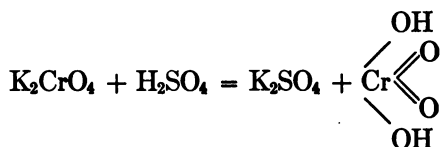
The exact nature of the process by which these accelerations of reactions is brought about is not known with cer-

tainty. The amount of acceleration depends upon the amount of surface of metal or oxide exposed to the reacting mixture, and it is known that platinum can absorb relatively large amounts of certain gases, and the more the greater the degree of fineness of its division. Since the more finely divided the metal the greater the surface exposed, the reason for the higher efficiency of the metal in a fine state of division becomes apparent. The catalytic action is most simply explained by assuming that the gases dissolve in the surface layer of the metal and therefore exist in much more concentrated state by which more molecules are brought together for interaction in a given time.

For the preparation of acetaldehyde, which is for brevity ordinarily referred to as aldehyde, in the laboratory the oxidation of alcohol is effected by chromic acid :



In this reaction the sulphuric acid first reacts with the potassium chromate, forming chromic acid :



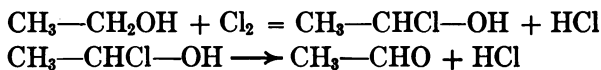
The chromium in the chromic acid gives up its oxygen to the alcohol, passing from the hexavalent to the trivalent state.

The green color of the chromous sulphate and the fruity odor of the aldehyde are so characteristic that this reaction

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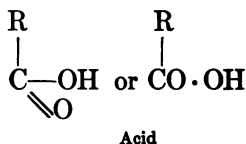
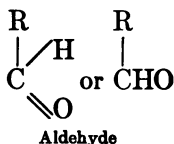
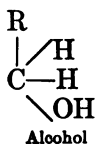
is employed reversably as a qualitative test for both chromic acid and for alcohol.

When chlorine is passed into a primary or secondary alcohol, hydrogen is replaced by chlorine, in a manner analogous to the behavior of hydrocarbons. The chlorine atom always replaces a hydrogen attached to the carbon atom which holds the hydroxyl group, *i.e.* to the carbon atom already linked to a negative group. The two negative groups cannot remain attached in this way, so the chlorinated alcohol has but a transitory existence. There results at once a separation of HCl and the formation of an aldehyde:

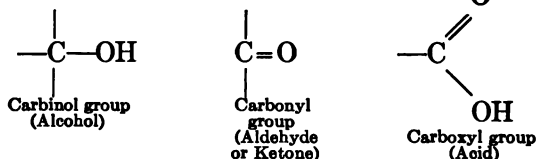


**31. Constitution of the Aldehydes and Acids.**—The relationship between the primary alcohols and their oxidation products, the aldehydes and acids, is shown by the following consideration: The primary alcohols correspond to the general formula  $\text{C}_n\text{H}_{2n+2}\text{O}$ ; the aldehydes to the formula  $\text{C}_n\text{H}_{2n}\text{O}$ , due to the loss of two hydrogen atoms through the first stage of oxidation; while the acids which result from the oxidation of the aldehydes correspond to the general formula  $\text{C}_n\text{H}_{2n}\text{O}_2$ .

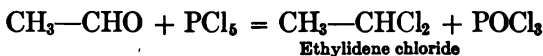
The constitutional formulæ assigned to these three classes of compounds are as follows:



The primary alcohols, the aldehydes and corresponding acids are derived from the hydrocarbons by the substitution of a hydrogen atom linked to a primary carbon atom by the following groups:



The behavior of these groups when acted upon by  $\text{PCl}_5$  throws further light upon their structure. Thus the alcohols yield, as already pointed out, alkyl halides, the OH acting as a unit and being replaced by Cl, a monovalent element. When  $\text{PCl}_5$  acts upon aldehydes, the oxygen is replaced by two Cl atoms forming dichlor hydrocarbons. With the organic acids  $\text{PCl}_5$  replaces the OH group as in the alcohols and leads to the formation of *acid chlorides*:

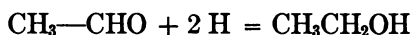


**32. Properties of the Aldehydes.** — (1) The aldehydes are characterized by exceptional chemical activity. They are easily oxidized, slowly by contact with the air and quickly by oxidizing agents such as chromic acid. They possess therefore marked *reducing properties*, and abstract oxygen from the oxides of the noble metals. They reduce an ammoniacal solution of silver oxide or silver salts, caus-

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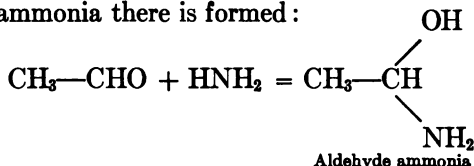
ing the deposition of metallic silver. Some of the aldehydes will likewise reduce alkaline copper solutions, especially in the presence of sodium hydroxide. This property is sufficiently characteristic and delicate to be of use as a reagent for detecting and estimating aldehydes (Fehling's solution).

(2) The aldehydes are easily reduced by nascent hydrogen to the same primary alcohols from which they are derived by oxidation :

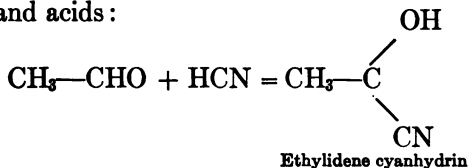


(3) Conversion into dichlor derivatives of the type  $\text{R—CHX}_2$  ( $\text{X} = \text{Halogen}$ ) (31).

(4) Addition reactions: (a) Aldehydes react with ammonia and hydrocyanic acid to form addition products. With ammonia there is formed :

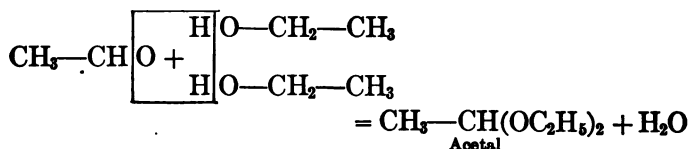


The addition reaction of aldehyde and  $\text{HCN}$  is of especial importance because it forms a method of building up synthetically compounds which are at the same time alcohols and acids :

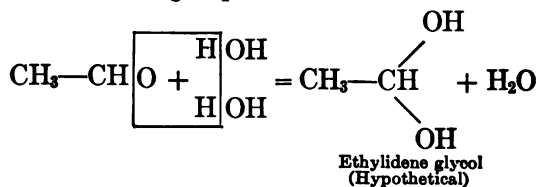


Ethylidene cyanhydrin is readily transformed into lactic acid (66).

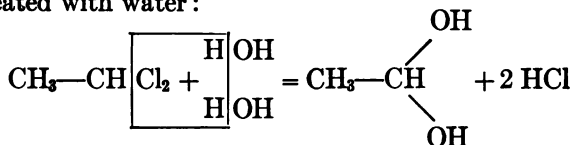
(b) Upon heating with alcohols, stable ethers—the “acetals”—are formed:



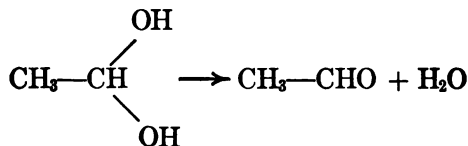
This reaction would lead to the supposition that the aldehydes could react with water to form dialcohols having both of the OH groups linked to one carbon atom:



This same compound, the hypothetical *ethylidene glycol*, we should expect to be formed when ethylidene chloride is heated with water:

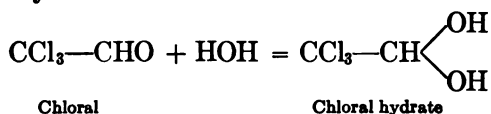


This does not appear to be the case. If it is formed its existence is but momentary, the compound being immediately broken down into the aldehyde and water:



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From such considerations the conclusion may be drawn that two hydroxyl groups cannot as a rule exist bound to the same carbon atom. A molecule of water is separated and an oxygen atom becomes bound to the carbon atom by both its affinities instead. When several negative atoms in the radical are introduced in place of hydrogen such hydrates can exist. Thus trichloroacetaldehyde, commonly called *chloral*, combines with water to form chloral hydrate:



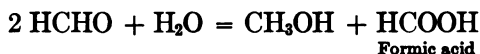
This compound does not behave like a diatomic alcohol, however, but like the aldehyde from which it was derived, owing to the ease with which water is separated.

(5) The aldehydes polymerize readily. By polymerization is meant the transformation of a compound into another having the same percentage composition with respect to the elements, but with a molecular weight which is a multiple of that represented by the simplest formula. In the case of formic aldehyde this change is spontaneous at the ordinary temperatures. Acetaldehyde does not polymerize so readily, but the change is brought about by the presence of traces of hydrochloric, sulphuric, or sulphurous acid, zinc chloride, etc. The reason for their catalytic effect is unknown.

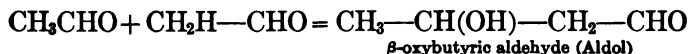
Alkalies induce a different kind of polymerization of aldehydes, leading to the formation of *aldehyde resins*. For acetaldehyde this is reddish brown in color, insoluble

in water, but soluble in alcohol, and gives off a peculiar odor which is characteristic.

Formic aldehyde, on the other hand, in the presence of alkali shows the phenomenon known as the *Cannizzaro reaction*, in which through the action of water one molecule of aldehyde is oxidized to acid, and another is reduced to an alcohol, thus :



(6) The aldehydes show a tendency to form condensation products in which two molecules combine with a rearrangement of the bonds of the carbon atoms, a hydrogen atom of one molecule changing its linkage from carbon to oxygen with the formation of a hydroxyl group. Thus when aldehyde stands in contact with acids or alkalies it undergoes what is known as the *Aldol condensation*. There is formed  $\beta$ -oxybutyric aldehyde :



This property of the aldehydes is of fundamental importance in biology, for the formation of carbohydrates, fats, proteins, etc., which occur in the animal and vegetable kingdoms.

Formic aldehyde does not condense through the influence of acids, but does so readily through the influence of very weak alkalies, even calcium carbonate greatly accelerating the action. The condensation products of formaldehyde will be considered in detail in connection with the synthesis of the sugars (151).

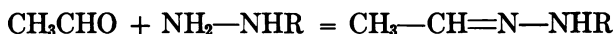


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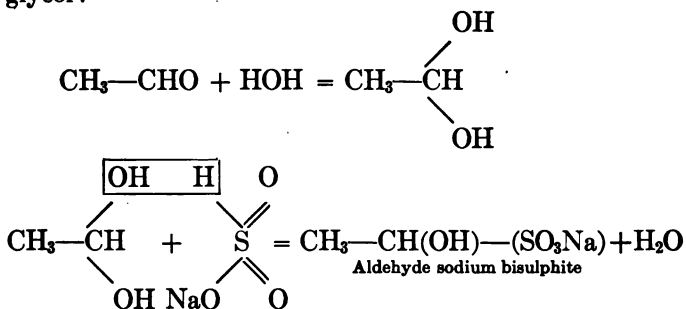
(7) With hydroxylamine,  $\text{NH}_2\text{OH}$ , aldehydes condense to form *aldoximes*, water being formed in the reaction:



(8) With hydrazine,  $\text{NH}_2\text{—NH}_2$ , or its substitution products, aldehydes condense to form *hydrazones*, compounds containing two nitrogen atoms:



(9) The aldehydes condense with sodium bisulphite to form crystalline compounds which are readily soluble in water, but sparingly so in alcohol. These are looked upon as sulphonic acid esters of the hypothetical ethylidene glycol:



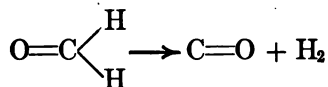
Such compounds are easily broken up on warming with a solution of sodium carbonate, with the re-formation of aldehydes. These compounds are of great importance, therefore, in the isolation of aldehydes.

*Nomenclature.*—The aldehydes are named from the hydrocarbons from which they are derived with the termination *-al*. Several of the more important ones have

long had names which do not correspond to this system of nomenclature.

**33. Formaldehyde.** —  $\text{H}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{H} \end{array}$  (Methanal). Results

from the regulated oxidation of methyl alcohol, employing a glowing platinum or copper spiral as a catalyzer (30). Other oxidizing agents acting on methyl alcohol do not yield the aldehyde. Instead the oxidation goes farther, formic acid being produced (50). It is a gas which when cooled strongly condenses to a liquid which boils at  $-21^{\circ}$ . Formaldehyde is formed by the direct union of hydrogen and carbon monoxide under the influence of the silent electrical discharge. At  $600^{\circ}\text{C}$ . it is again dissociated into hydrogen and carbon monoxide:



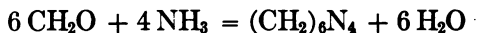
This is an example of the change of carbon from the divalent into the tetravalent state and vice versa. This type of change in the nature of carbon will be further treated under the isonitriles (40). Formaldehyde is supplied commercially as a 40 % solution known as formalin.

Formaldehyde is a powerful poison by reason of its power to condense with the proteins of the tissues, destroying their special properties as components of the living protoplasm. It is employed in disinfection and in the preservation and hardening of anatomic specimens.

With ammonia it forms hexamethylenetetramine, or *urotropin*, a feebly basic crystalline solid, soluble in 1.8

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parts of water and 10 parts of alcohol. (Sometimes also called aminoform and cystamin.)



It is employed internally in medicine as an antiseptic. It is absorbed without decomposition and passes through the kidneys in great measure unchanged, but the urine after its administration frequently contains traces of formaldehyde.

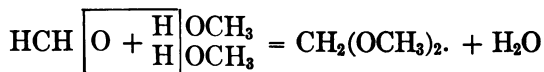
*Polymerization of formaldehyde.*—According to the conditions formaldehyde polymerizes in different ways.

*Paraldehyde* is formed when formalin is evaporated on a water bath. It is a white solid which melts at about  $153^\circ$  and on strongly heating evolves formaldehyde. It is looked upon as  $(\text{CH}_2\text{O})_2$ .

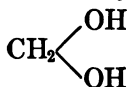
*Trioxymethylene*  $(\text{CH}_2\text{O})_3$  is a white crystalline compound which separates from solutions of formaldehyde on standing. This substance differs from paraldehyde in that it does not dissolve in water, alcohol, or ether. It is formed spontaneously when formaldehyde solution is allowed to evaporate at ordinary temperatures. It passes into formaldehyde again on heating.

*Formose*  $(\text{CH}_2\text{O})_6$  is a condensation product resulting from the action of milk of lime on formaldehyde. It consists of a mixture of sugars of the glucose group (151).

**Methylal**,  $\text{CH}_2(\text{OCH}_3)_2$ , may be looked upon as derived from one molecule of formaldehyde and two of methyl alcohol:



It is therefore an ether of the hypothetical glycol



It is employed as a soporific and anesthetic, B. P. 42°. It is soluble in water, in alcohol, and in oils.

**Acetaldehyde** (*acetic aldehyde, ethanal, aldehyde*),  $\text{CH}_3\text{CHO}$ . The preparation of this aldehyde by the oxidation of alcohol has already been described (30). It is purified by conversion into aldehyde ammonia, which is filtered and washed with ether. The aldehyde ammonia is afterward distilled with dilute sulphuric acid.

It is obtained in large quantities as a by-product in the distillation of fermented solutions in the manufacture of spirits. It is a colorless liquid, B. P. 21°, specific gravity about .8. It has a characteristic suffocating odor. It is a solvent for sulphur, phosphorus and iodine. Aldehyde dissolves readily in water, alcohol, and ether.  $\text{PCl}_5$  converts it into ethylidene chloride (31).

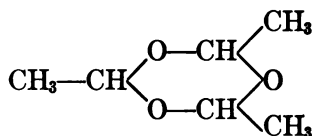
*Paraldehyde*  $(\text{C}_2\text{H}_4\text{O})_3$  is formed when a little  $\text{HCl}$ ,  $\text{COCl}_2$ ,  $\text{SO}_2$ , or  $\text{ZnCl}_2$  is added to aldehyde. It is formed with a violent reaction on adding concentrated sulphuric acid to aldehyde.

It is a colorless liquid which crystallizes below 10.5°, B. P. 124°. It possesses a peculiar, aromatic, suffocating odor and a warm taste; is soluble in alcohol, ether, oils and chloroform, and in ten parts of water. Specific gravity, .995 at 15°.

Paraldehyde is a hypnotic and antispasmodic, and is used in medicine to a considerable extent.

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Paraldehyde has the constitution :



It reacts in the same way as aldehyde with  $\text{PCl}_5$ , but does not react with hydroxylamine, ammonia, or sodium bisulphite. The ease with which paraldehyde is reconverted into aldehyde by distillation with dilute sulphuric acid is taken as evidence that the carbon atoms are linked through oxygen and not carbon directly to carbon. The bond between two carbon atoms is much too stable to be broken in this manner.

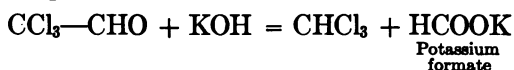
*Metaldehyde* ( $\text{C}_2\text{H}_4\text{O}$ )<sub>3</sub> is formed by the action of gaseous  $\text{HCl}$  or  $\text{SO}_2$  in aldehyde cooled to the temperature of a freezing mixture. It is a white crystalline substance, insoluble in water, soluble in chloroform, benzene, slightly soluble in alcohol and in ether. It sublimes at  $112-115^\circ$  with partial conversion into aldehyde. It is employed as a hypnotic and sedative.

Aldehyde ammonia,  $\text{CH}_3-\text{CH} \begin{array}{l} \diagup \text{OH} \\ \diagdown \text{NH}_2 \end{array}$ , is prepared by

passing dry ammonia gas into a solution of aldehyde in ether. It forms white crystals which are readily soluble in water, but slightly soluble in ether; M. P.  $70-80^\circ$ . It distills undecomposed at  $100^\circ$ .

**34. Chloral**, *Trichloroacetaldehyde*,  $\text{CCl}_3-\text{CHO}$ , a liquid with a sharp and characteristic, disagreeable odor, B. P.  $98^\circ$ , is formed as the end product of the action of

chlorine on alcohol. When impure it easily changes to a crystalline solid polymerization product, metachloral, but is converted back into chloral on heating. It is readily oxidizable to trichloroacetic acid. With alkalis it is decomposed into chloroform and a salt of formic acid:



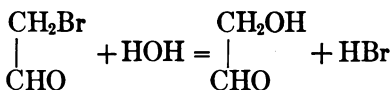
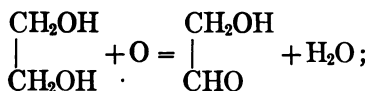
Chloral readily adds a molecule of water, forming *chloral*

*hydrate*,  $\text{CCl}_3\text{—CH} \begin{matrix} \text{OH} \\ \text{OH} \end{matrix}$ . This is a crystalline substance

soluble in water, which melts at 57°, and boils at 97° with dissociation into chloral and water. It is employed as a soporific and antiseptic. Strong sulphuric acid withdraws a molecule of water from it, forming chloral.

35. **Glycol Aldehyde**,  $\begin{matrix} \text{CH}_2\text{OH} \\ | \\ \text{CHO} \end{matrix}$ , may be regarded as oxy-

acetaldehyde or as the half aldehyde of glycol. It shows the properties of both an alcohol (12) and an aldehyde. It is formed by the oxidation of glycol or by the reaction of brom acetaldehyde with barium hydroxide:



It is a sweet, crystalline compound and is the simplest substance having the properties of the sugars (see carbohydrates, 150).

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**Glyoxal**,  $\begin{array}{c} \text{CHO} \\ | \\ \text{CHO} \end{array}$ , results from the oxidation of glycol or

may be prepared by oxidizing acetaldehyde with nitric acid at ordinary temperatures. It is not crystallizable, but is a solid when free from water. It forms a bisulphite compound which is useful in its isolation.

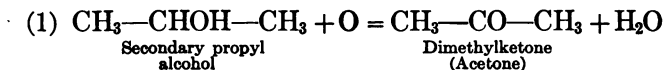
**36. Glyceraldehyde**,  $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CHOH} \\ | \\ \text{CHO} \end{array}$ , results from the oxidation

of glycerol by sodium hypobromite or by hydrogen peroxide in the presence of ferrous sulphate. There is

always formed with it the isomeric compound,  $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CO} \\ | \\ \text{CH}_2\text{OH} \end{array}$   
Dihydroxyacetone

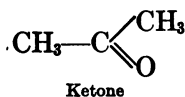
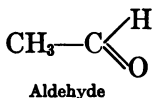
the latter representing the principal product of the oxidation. Glyceraldehyde can also be prepared from acrylic aldehyde (85), which confirms its structure.

**37. Ketones.** — When secondary alcohols are oxidized they lose two hydrogen atoms and yield ketones, compounds containing the carbonyl group in a secondary position :

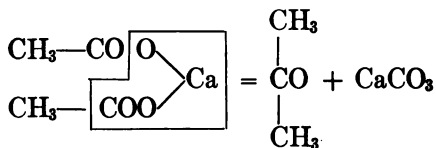


They contain the carbonyl group linked to two carbon atoms, and may be looked upon as aldehydes in which the

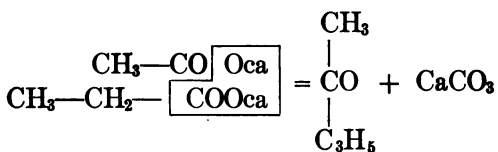
H of the CHO group has been replaced by an alkyl group, or as organic acids whose hydroxyl is exchanged for alkyl. The existence of ketones having less than three carbon atoms is theoretically not possible.



(2) Acetone,  $\text{CH}_3-\text{CO}-\text{CH}_3$ , is also formed by the dry distillation of the calcium or barium salt of acetic acid :



(3) By employing acids having longer carbon chains ketones with higher alkyl groups are formed. Thus a mixture of equal molecules of calcium acetate and calcium propionate,  $\text{CH}_3-\text{CH}_2-\text{COOca}$  ( $\text{ca} = \frac{1}{2} \text{Ca}$ ), yields a mixed ketone :

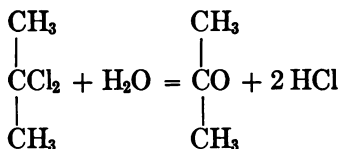


(4) Alkyl dichlorides of the type  $\begin{array}{c} \text{R} \\ | \\ \text{CCl}_2 \\ | \\ \text{R} \end{array}$  react with

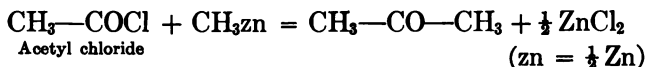
water to form ketones :



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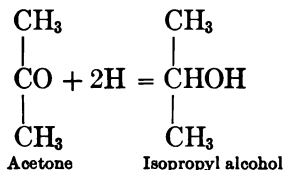


(5) Zinc alkyl reacts with the acid chlorides, forming ketones:



*Nomenclature.* — The name of the alkyl radical followed by the ending ketone indicates the structure of these compounds, as dimethyl, diethyl, methyl-ethyl ketone, etc. This also indicates the isomerism among the ketones, which may be due to: (a) The alkyl groups having the normal or branched structure, or (b) to the position of the CO group in similar carbon chains. Thus a ketone containing six carbon atoms may be methyl-butyl ketone, or ethyl-propyl ketone,  $\text{CH}_3\text{—CO—C}_4\text{H}_9$ , or  $\text{C}_2\text{H}_5\text{—CO—C}_3\text{H}_7$ .

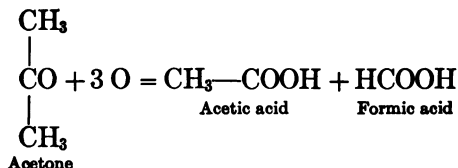
*Chemical Behavior.* — (1) The ketones, like the aldehydes, are reducible to the alcohols from which they are formed on oxidation, thus:



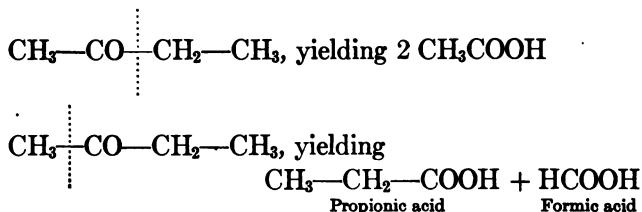
Ketones yield on reduction therefore secondary alcohols.

(2) Ketones differ markedly from aldehydes in their behavior toward oxidizing agents. They yield acids having

a lesser number of carbon atoms than the ketones themselves, whereas the aldehydes yield acids of the same number of carbon atoms, thus :



Methyl-ethyl ketone may be oxidized in two ways, thus :



Under the influence of oxidizing agents, as chromic acid, as well as in the animal body, the cleavage of the carbon chain in such compounds never follows one line to the exclusion of all others. There results a certain amount of each of the possible oxidation products. In the case of methyl-ethyl ketone, formic, acetic, and propionic acids would be formed, but not necessarily in equivalent amounts.

(3) The ketones are converted by  $\text{PCl}_5$  into dichlorides of the type  $\text{R}_2\text{=CCl}_2$ . It has been pointed out above that these can react with water with the re-formation of ketones.

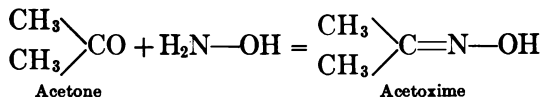
The carbonyl group of the ketones shows less tendency to unite with water and with alcohol than in the case of

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the aldehydes. With hydrocyanic acid, however, there are formed addition products called nitriles. These compounds are of the greatest importance in synthetic chemistry. They will be dealt with in detail later (40, 156).

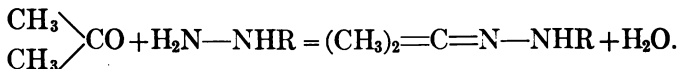
(4) The ketones differ from the aldehydes in that they do not polymerize. They do form condensation products, however, analogous to the behavior of aldehydes. Acetone, when acted upon by HCl, H<sub>2</sub>SO<sub>4</sub>, KOH, CaO, and other reagents, condenses with the separation of water. Two molecules unite to form mesityl oxide, C<sub>6</sub>H<sub>10</sub>O; three molecules condense to form mesitylene (172).

(5) Like the aldehydes, the ketones condense with hydroxylamine to form ketoximes (31).

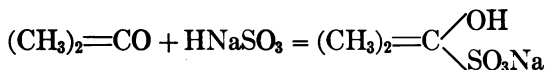


Acetoxime on heating with concentrated HCl decomposes into acetone and hydroxylamine.

In a similar manner, ketones condense with the amino group of the hydrazines, forming hydrazones:



Those ketones which contain the radical CH<sub>3</sub>—CO—, and a few others, form addition products with sodium bisulphite in a manner similar to the aldehydes:



These when heated with sodium carbonate solution regenerate ketones. These compounds are of great value in separating ketones from mixtures and in purifying them.

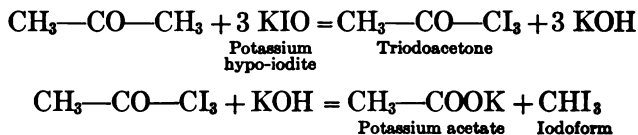
**38. Acetone**,  $\text{CH}_3\text{—CO—CH}_3$ , is the simplest and most common ketone. It is a liquid with a characteristic ethereal odor, B. P.  $56^\circ$ .

Its specific gravity at  $0^\circ$  is 0.81. It is soluble in water, but much less so in solutions of inorganic salts. This property is made use of in separating it from water solutions. It likewise dissolves in all proportions in alcohol and in ether.

It is a very stable substance toward oxidizing agents, not being attacked by cold  $\text{KMnO}_4$  solutions, but it is oxidized to acetic and formic acids by chromic acid. It is very inflammable and should be handled with caution against the ignition of its vapors. Acetone occurs in normal urine in very small amounts, but is present in large quantities in the urine of diabetic patients. Its formation in the body will be explained later (see acetoacetic acid, 127).

Lieber's iodoform test for acetone depends upon the fact that alkaline iodine solutions oxidize acetone and form triiodo methane or iodoform. A solution of iodine and KI is added to the solution to be tested and then dilute sodium hydroxide added drop by drop. The iodine color is discharged at once and there separates at once a crystalline deposit of iodoform. The reactions involved are:

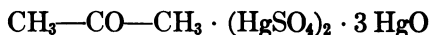
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The iodoform can be extracted with ether, and on evaporation of the latter is left as yellow hexagonal plates having a characteristic odor. On the formation of iodoform under these conditions depends the qualitative detection of acetone devised by Vournasos. This test is not characteristic for acetone but is given by alcohol and aldehyde as well.

Acetone in the presence of alkali dissolves mercuric oxide, and this property is made use of in testing for its presence in solution. A mercuric salt, as the chloride or nitrate, is added to the solution to be tested, and then sodium hydroxide to strong alkalinity, and then an equal volume of alcohol. The solution is then filtered and the filtrate acidified with HCl and a layer of  $(\text{NH}_4)_2\text{S}$  solution poured carefully upon it. If mercury is precipitated as the black sulphide, it indicates a positive test. Aldehydes also give this reaction.

Acetone forms with mercuric oxide the compound  $2 \text{CH}_3\text{—CO—CH}_3 \cdot 3 \text{HgO}$ , insoluble in dilute acetic acid; also a white crystalline compound,

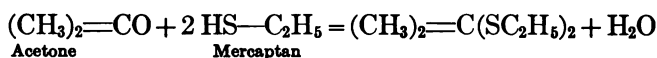


The latter compound is very insoluble in dilute acetic acid, and its formation is the basis of the test for acetone designed by Deniges.

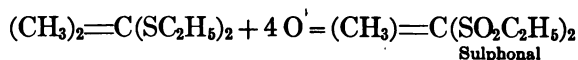
Acetone does not reduce Fehling's solution. With

o-nitro benzaldehyde and sodium hydroxide acetone reacts to form indigo (326).

**Sulphonal**, a substance used as a soporific, is derived from the condensation product of acetone and mercaptan. When these are mixed and treated with hydrochloric acid they condense with the separation of water :

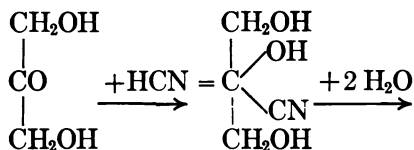


On oxidation this product yields a disulphone, which is *sulphonal*.

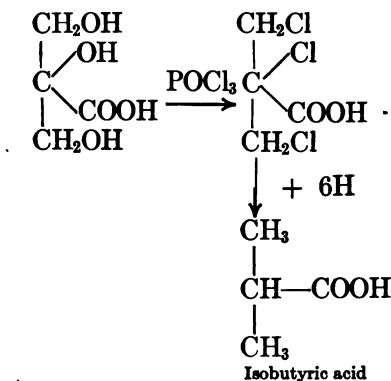


Several derivatives of higher ketones have also been introduced. Trional is made from ethyl-methyl ketone, and tetronal contains four ethyl groups.

**39. Dihydroxyacetone**,  $\text{CH}_2\text{OH}-\text{CO}-\text{CH}_2\text{OH}$ , results from the oxidation of glycerol with sodium hypobromite or nitric acid. Its formation is accompanied with that of its isomer glyceraldehyde (36). The structure of dihydroxyacetone is established by the fact that it forms, with hydrocyanic acid, an oxynitrile (32) which by chlorination and subsequent reduction is converted into *isobutyric acid* :



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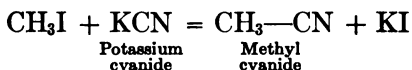


Dihydroxyacetone is chemically related to the sugars (150).

## CHAPTER V

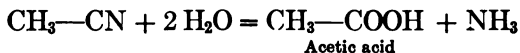
### THE NITRILES AND THEIR REDUCTION PRODUCTS, THE AMINES

**40. The Nitriles and Isonitriles.** — It has been pointed out (28) that alkyl halides react with certain salts of acids, yielding esters, and that these on hydrolysis are resolved into alcohols and acids. The behavior of the salts of hydrocyanic acid is different from others in that it yields two classes of derivatives which do not go back into alcohol and hydrocyanic acid, but yield a new type of compound on hydrolysis :

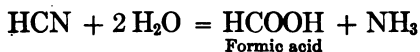


*Methyl cyanide* is a colorless liquid boiling at 81°. Its specific gravity is .805 at 0°. It is soluble in water and is combustible.

On being warmed with either acids or alkalies nitriles add water (saponification) and are converted into acid and ammonia :



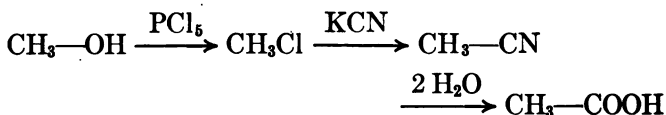
This behavior is analogous to that of hydrocyanic acid, which when heated with dilute acids is converted into formic acid and NH<sub>3</sub> :





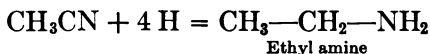
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Aside from the importance of the nitriles for the formation of acids they are of the greatest importance for building up carbon chains. Thus any alcohol can be converted by  $\text{PCl}_5$  into its alkyl halide derivative, and this on being converted into a nitrile gains a new carbon atom :



Two practices prevail regarding the nomenclature of the alkyl cyanides. They are called methyl cyanide, ethyl cyanide, propyl cyanide, etc., but are more frequently called nitriles, and are then named after the acid which they yield on hydrolysis.  $\text{CH}_3\text{—CN}$  is called acetonitrile ;  $\text{CH}_3\text{—CH}_2\text{—CN}$ , propionitrile, etc.

Nascent hydrogen reduces the nitriles to compounds called amines. The process is one of addition of hydrogen :

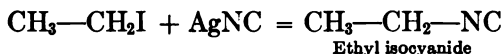


The amines may be looked upon as ammonia in which one hydrogen atom is replaced by an alkyl group (see amines, 43).

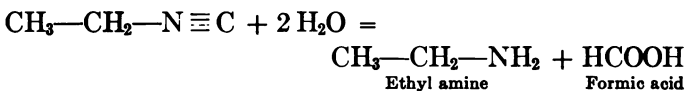
The formation of carboxyl and ammonia on hydrolysis and of amines on reduction shows that in the nitrile the nitrogen cannot be directly linked to the alkyl radical. The CN group is linked to the alkyl group by its carbon.

*Isonitriles.* — If instead of KCN we cause alkyl halide to react with silver cyanide, there is obtained a colorless liquid slightly soluble in water which has an intolerable

odor and poisonous properties. It has the same percentage composition with respect to the elements as ethyl nitrile, and is isomeric with it:



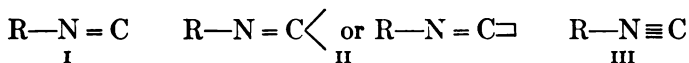
This substance behaves on heating with water or with acids in a manner entirely different from ethyl cyanide:



In this compound the carbon atom of the isocyanide is split off, which indicates that the nitrogen is linked directly to the ethyl group. Unlike the nitriles they are very stable toward alkalis.

From the above considerations it appears that the silver salt of hydrocyanic acid has a structure different from that of potassium cyanide.

A great interest attaches to the isonitriles or alkyl isocyanides because they apparently form an exception to the general rule that carbon in organic compounds is always tetravalent. Several possible assumptions may be made regarding the structure of these compounds. The carbon atom may be in a divalent state (I); or two of its valences may be free, or polarized (II); or the nitrogen may exist in the pentavalent state (III) as it is known to be, *e.g.*, in ammonium hydroxide, all four valences of the carbon atom being in union with nitrogen.

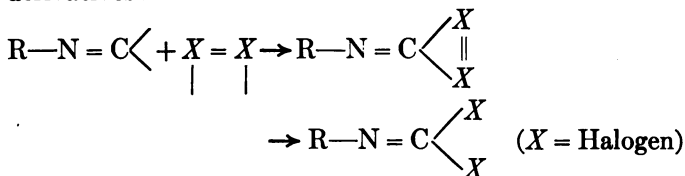


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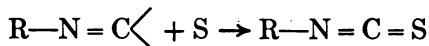
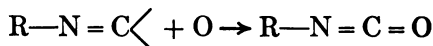
The extensive studies of Neff have afforded the most satisfactory explanation of the structure of the isonitriles, and the principles which they disclosed are of great importance in elucidating the nature of reactions generally among organic compounds. A discussion of some reactions which throw light on the behavior of these compounds will be of value.

The isonitriles are assumed by Neff to possess the structure represented by  $R-N=C$ , but there exists a small number of the molecules dissociated into the "active" form  $R-N=C\angle$ , these being in dynamic equilibrium with the form  $R-N=C$  which, either because its carbon is divalent, or because two of its bonds of affinity are polarized or latent, is incapable of any chemical activity whatever. The percentage of "active" molecules varies with the nature and mass of R, a fact shown by the variation in the chemical activity of compounds of this type.

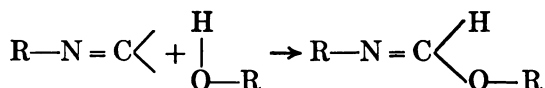
1. Halogens (chlorine, bromine, iodine), speed of reaction in the order named, are absorbed by the alkyl isocyanides with great evolution of heat, forming dihalogen derivatives:



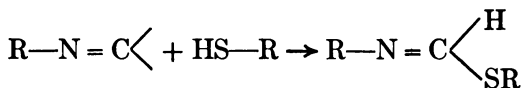
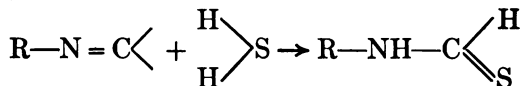
2. Oxygen and sulphur convert the isocyanides into isocyanates and isothiocyantes respectively:



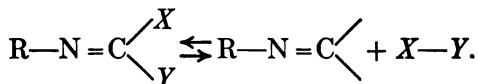
3. Alcohols in the presence of alkali are absorbed, giving compounds known as imido ethers:



4. Hydrogen sulphide and mercaptans give the addition products:



A striking property of these addition products of the isonitriles is their low point of dissociation, *i.e.* the carbon atom which has absorbed the  $X-Y$ , thus becoming tetravalent, is unable to hold  $X-Y$  above certain temperature limits. There is therefore a certain temperature, varying with the nature of all the groups in the compound, at which the carbon atom becomes spontaneously divalent, the  $X-Y$  becoming dissociated, thus:

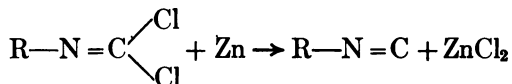


The dissociation is very slight at low and moderate temperatures and increases as the temperature is raised.

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There is an equilibrium between divalent and tetravalent carbon.

Dynamic equilibrium implies a set of conditions in which if one of the components of a system is withdrawn, it is replaced by the further dissociation of a part of the undissociated component, so that a definite relationship always exists among the components of the system. Thus the dihalogen addition products of the alkyl isocyanides are converted back into the alkyl isocyanides if kept in contact with zinc dust, the latter serving simply to tie up progressively and remove from the system the small amount of halogen which is dissociated. The dissociation becomes progressive under these conditions and the reaction goes to completion:



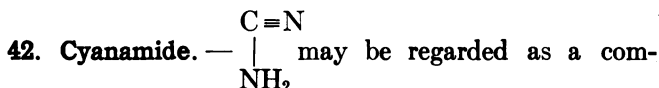
The isonitriles have a marked tendency to polymerize and form resinous products. This is without doubt due to the combination of the active dissociation products with each other, the reaction in this case being non-reversible.

**41. Fulminic Acid.** — When KCN is oxidized there is produced potassium cyanate, KCNO. There appears to exist an acid isomeric with cyanic acid in fulminic acid. The free acid is not known in a state of purity, but its salts, especially the mercuric and the silver fulminates, are well known. The formulæ for these compounds correspond to  $\text{Hg}(\text{ONC})_2$  and  $\text{AgONC}$ .

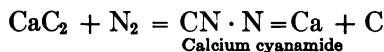
On hydrolysis the fulminates yield hydroxylamine and a salt of formic acid :



The formula HONC for fulminic acid can be accepted only by assuming the existence of carbon in a divalent form. This assumption is not ordinarily considered tenable, but there is one compound of carbon, viz. carbon monoxide, which must certainly contain divalent carbon.



pound in which a hydrogen of ammonia is replaced by the cyanide radical. The latter is strongly negative and exerts an influence upon the behavior of the hydrogen atoms of the  $\text{NH}_2$  group. While ammonia is capable of forming metallic derivatives, these are not readily formed. Sodium and potassium must be strongly heated in the presence of ammonia before the *amides* of these metals are formed ( $\text{NaNH}_2$ ,  $\text{KNH}_2$ ) and magnesium must be heated to incandescence in order to form the *nitride*. The hydrogen atoms of the  $\text{NH}_2$  or *amide group* in cyanamide are much more easily replaced by metals. Silver cyanamide,  $\text{AgHN}-\text{C} \equiv \text{N}$ , is a yellow amorphous compound, formed by adding soluble silver salts to solutions of cyanamide. Cyanamide is obtained as the calcium compound by passing nitrogen over heated calcium carbide :



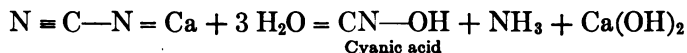
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It is now made on a large scale and is used as a fertilizer.

Calcium cyanamide is slowly decomposed by water, forming calcium carbonate and ammonia :



As an intermediate product cyanic acid is formed :



Cyanic acid readily reacts with water to form ammonia and carbon dioxide :



Cyanamide is a crystalline compound readily soluble in water, alcohol, and ether. It melts at 40°.

**43. The Amines.** — The hydrogen atoms of ammonia may be replaced by alkyl groups, forming a class of compounds called amines, which have a great biological importance. Many of them occur in nature, especially as products of the action of putrefactive bacteria on proteins. The amines containing the lower alcohol radicals closely resemble ammonia in odor and are even more strongly basic than the latter. Like ammonia, they form white clouds of finely divided salts when brought into contact with volatile acids. The union with acids is attended with the evolution of heat. They behave like ammonia in forming double salts with salts of the heavy metals such as platinic or gold chloride.

They differ from ammonia in being combustible. The lower members are readily soluble in water. The solubility in water diminishes with increasing length of the carbon

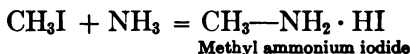
chains. The volatility likewise diminishes with increasing molecular weight, the highest members being solids insoluble in water and without odor. These are, however, still soluble in alcohol and ether and are basic in character, readily combining with acids to form salts. The specific gravity of all the amines is considerably less than that of water.

*Classification.* — The amines are termed primary, secondary, or tertiary, depending on whether one, two, or three hydrogen atoms of ammonia are replaced by alkyl groups,

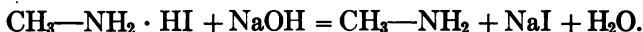


The characteristic group of the primary amines is therefore  $\text{—NH}_2$ , of the secondary amines  $\text{=NH}$ , and of the tertiary amines  $\equiv\text{N}$ .

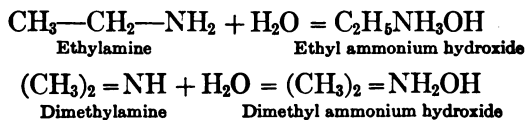
The relation of the amines to the hydrocarbons is shown by their synthesis from the alkyl halides and ammonia :



Methyl ammonium iodide is a salt entirely analogous to ammonium iodide. On the treating this salt with an alkali, methyl amine is liberated :



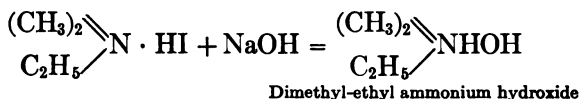
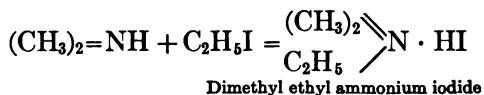
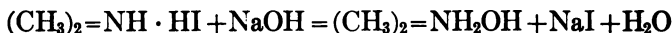
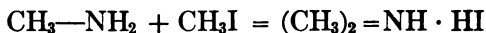
The amines show their character as substituted ammonias in uniting with water to form hydroxides :



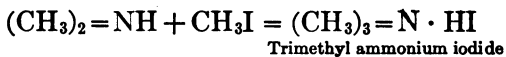


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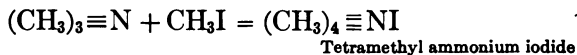
The secondary amines are formed from the primary by the further action of alkyl halide :



Trimethylamine is formed by the action of alkyl halide upon dimethylamine :



Trimethyl ammonium iodide on treatment with an alkali yields trimethylamine in a manner analogous to the primary and secondary compounds. Trimethylamine can likewise take up a molecule of methyl halide (or other alkyl halide) and form tetramethyl ammonium iodide :



These compounds are known as quaternary bases. They are not capable of reacting with hydroxides of the alkali metals. They are so stable that they can be boiled with sodium hydroxide without decomposition. The liquid and gaseous amines are volatile with steam, as is ammonia, but the ammonium bases or quaternary bases are not volatile.

The above described reactions for the formation of the primary, secondary, and tertiary bases were written as if only one product was formed in each case, *e.g.* methylamine from methyl halide and ammonia. This does not represent what actually takes place, however, for in practice it is found that even though equimolecular quantities of these two substances be brought into reaction, not only is methylamine, which is the principal product, produced, but all the other possible methylamines, as well, although in much smaller amounts.

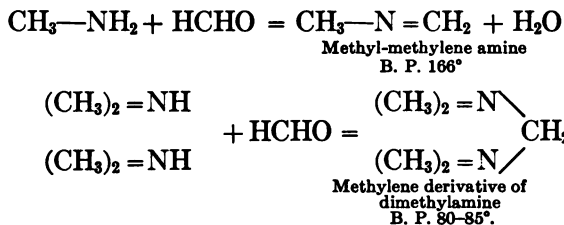
**44. Separation of Amines and Ammonia.**—Ammonia can be removed quantitatively from its mixtures with the amines by a method described by Erdmann. The solution containing both classes of compounds (*e.g.* the distillate obtained in the Kjeldahl nitrogen determination) is made strongly alkaline with a mixture of sodium hydroxide and sodium carbonate and yellow mercuric oxide (*i.e.* the oxide in a very fine and amorphous state) added. There results on standing a reaction:



The alkyl ammonias or amines do not react with mercuric oxide in this way. The mercuric ammonium hydroxide is practically insoluble in water and can be filtered off, leaving the amines in solution.

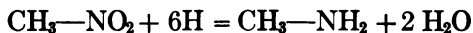
Delepine has proposed a method for separating the primary, secondary, and tertiary amines which depends upon the fact that the primary and secondary condense with formaldehyde, while the tertiary amines do not:

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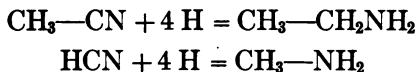


The wide difference in the boiling points of these two compounds makes possible their separation. The bases can be regenerated from the methylene compounds by hydrolysis.

**45. Methods of Preparation.**—(1) The nitro derivatives of the hydrocarbons are reduced by nascent hydrogen, yielding primary amines :



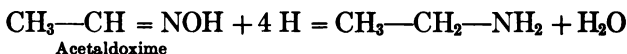
(2) The nitriles, including hydrocyanic acid, can take up four atoms of hydrogen, passing into primary amines :



(3) Hydrolysis of alkyl isocyanides yields primary amines and formic acid (40).

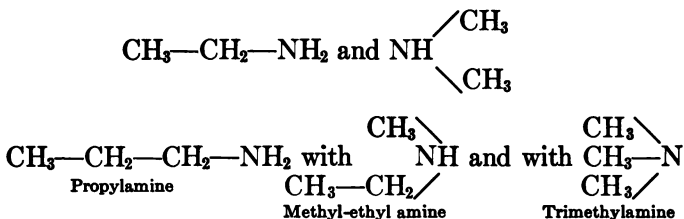
(4) The action of alkyl halides on ammonia has already been referred to (43).

(5) The oximes (32) are reduced by nascent hydrogen with the formation of primary amines :



(6) From acid amides by the action of bromine and sodium hydroxide (53).

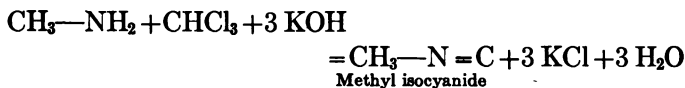
46. *Isomerism of the Amines.*—Two types of isomers of the amines should be mentioned. One is like the isomerism of the ethers, viz. metamerism. Thus :



The other depends upon the presence of normal or branched carbon chains as in the alcohols (9).

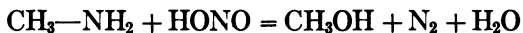
*Chemical Behavior.*—(1) The amines are not decomposed by saponifying agents, as acids and alkalies, and are oxidized only with great difficulty.

(2) A reaction which distinguishes the primary from the secondary and tertiary amines is their behavior with chloroform. The primary amines react with  $\text{CHCl}_3$  and alcoholic potassium hydroxide, with the formation of isonitriles. The characteristic odor of the isonitriles (40) serves as a delicate qualitative test :



This is known as Hoffman's carbylamine reaction.

(3) Nitrous acid reacts with primary amines, replacing the  $\text{—NH}_2$  group by hydroxyl,  $\text{—OH}$ . Elementary nitrogen is liberated from the amino group :

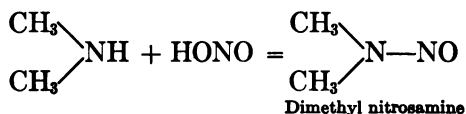


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This reaction is of great importance in synthetic chemistry, since it makes possible the conversion of amines into the corresponding alcohols.

Recently it has assumed great importance in the eyes of physiological chemists as the result of the discovery by Van Slyke of the conditions necessary for making this reaction the basis of a simple and highly accurate quantitative estimation of amino groups.

With the secondary amines no elementary nitrogen is formed from the imino group  $=\text{NH}$ . Instead there are formed *nitrosamines*:



Dimethyl nitrosamine is an oil with a yellowish color which is readily volatile with steam and can be separated from its mixtures in this way.

Tertiary amines are not acted upon by nitrous acid.

**47. Methylamine**,  $\text{CH}_3\text{—NH}_2$ , occurs in *Mercurialis perennis* and in the distillate from bones and wood and in herring brine and putrefaction mixtures. It also appears to be a normal constituent of urine, but in very small amounts. It is a gas which greatly resembles ammonia, but its odor is also distinctly fish-like. It is even more strongly basic than ammonia. Its mixtures with air are explosive, and it burns with a yellow flame, in which it differs from ammonia, which is not combustible. One volume of water dissolves at  $12.5^\circ$  1150 volumes of the gas. It precipitates as double salts the salts of platinum and

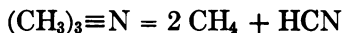
gold, and behaves like ammonia in forming methylated ammonium magnesium phosphate, analogous to the ammonium compound.

Methylamine gives with Nessler's reagent (a solution of  $\text{HgI}_2$  and  $\text{KI}$  in potassium hydroxide) a precipitate which is insoluble in an excess of the reagent, or of water. This characteristic serves to distinguish it from the secondary and tertiary amines.

*Dimethylamine* occurs among the distillation products of wood (pyroligneous acid, 51) and in guano. It boils at  $7^\circ$ .

*Trimethylamine*,  $(\text{CH}_3)_3\text{N}$ , is found in certain plants, as *Chenopodium vulvaria* and *Arnica montana*, in ergot, and elsewhere. It is a decomposition product of betaine (63) and similar plant bases and also of choline (48), and results from the action of putrefactive bacteria on materials containing these substances, or through destructive distillation of the same, as in the distillation of vinasse. Some investigators have reported finding traces of trimethylamine in urine, but in the light of recent studies with improved methods it appears that fresh normal urine of man or animals does not contain this base. It has an odor resembling ammonia, but also fish-like. It boils at  $3.2^\circ$ . Its preparation has been described (43).

Trimethylamine breaks up when strongly heated, forming methane and hydrocyanic acid:



*Ethylamine*,  $\text{C}_2\text{H}_5\text{—NH}_2$ , is formed from alanine (69) by destructive distillation, and possibly also by the action of

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anaërobic bacteria on the same, but its origin through the latter agency has not been demonstrated. It has little biological importance.

*Oxyethylamine*,  $\text{CH}_2\text{OH}-\text{CH}_2-\text{NH}_2$ , has been found among the products of hydrolysis of lecithin (96).

Aside from those mentioned the most important aliphatic amines are the following:

*Isobutylamine*,  $\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH}-\text{CH}_2-\text{NH}_2 \\ \diagup \\ \text{CH}_3 \end{array}$ , is a liquid

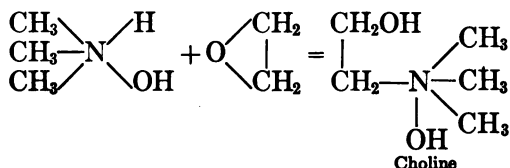
which boils at  $68^\circ$ . It mixes with water in all proportions. It is formed by putrefactive bacteria acting on amino isovaleric acid, one of the digestion products of the proteins. Its formation will be described later (73). It differs from the primary amines having lower alkyl groups in that it causes a rise of blood pressure in animals.

*Isoamylamine*,  $\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH}-\text{CH}_2-\text{CH}_2-\text{NH}_2 \\ \diagup \\ \text{CH}_3 \end{array}$ , boils at

$95^\circ$ . It results from the putrefaction of proteins, being derived from the amino acid leucine (75); also on sterile self-digestion (autolysis) of the mushroom, *Boletus edulis*, doubtless formed from leucine. When intravenously injected it raises the blood pressure. With hydrochloric acid it forms a salt, isoamylamine hydrochloride, which is employed to some extent as an antipyretic. Both the free base and its hydrochloride are soluble in water.

**48. Choline** is a base of great physiological interest, since it occurs in all cells of both animals and plants and is especially abundant in nervous tissue. It does not occur

free in appreciable amount under normal conditions in the animal body, but may accumulate in the cerebrospinal fluid under certain pathological conditions, in which degeneration of nervous tissue is taking place. Choline is always a constituent of certain compounds related to the fats, called *lecithins* (96), which are present in large amounts in brain tissue and in egg yolk. From its mode of synthesis it is shown to be a derivative of glycol (22), and trimethylamine. It is formed by the condensation of trimethyl ammonium hydroxide with ethylene oxide (23).



The group  $-\text{CH}_2-\text{CH}_2\text{OH}$  may be called *oxyethyl*. The name of choline, considering it as a substituted ammonium hydroxide, is trimethyl-oxyethyl-ammonium hydroxide.

Choline is a strong base. In the free state it absorbs moisture and  $\text{CO}_2$  readily from the air. Its solutions may be concentrated by boiling to 4 %, when it decomposes into trimethylamine and glycol. Choline is precipitated by a number of reagents, the most efficient being potassium periodide, which precipitates 1 part in 2,000,000 of water.

Choline possesses no marked physiological action, but by the action of bacteria and of chemical reagents which abstract water, a base *neurine* is formed, which is 10–20 times more toxic than is choline itself (97).



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Other amines of physiological importance can best be described in their relations to the amino acids.

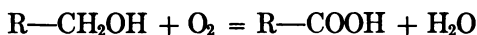
**49. Physiological Action of the Amines.** — Whereas ammonia, intravenously injected, produces tetanic convulsions, with quickening of the heart and respiration, the amines resulting from the replacement of the hydrogen of ammonia by the aliphatic hydrocarbons have but a slight physiological action, although they irritate the mucous membranes. The convulsant effect of ammonia diminishes progressively as the hydrogen atoms are successively substituted, dimethylamine being less toxic than methylamine, etc.

When the tertiary amines pass over to ammonium compounds, *i.e.* the nitrogen changes from the trivalent to the pentavalent state, a great increase in toxicity occurs. These substances resemble many of the alkaloids in their properties.

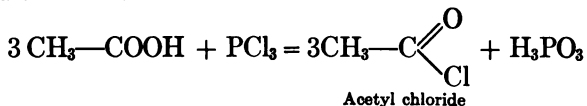
## CHAPTER VI

### THE FATTY ACIDS

50. It has been pointed out in connection with the aldehydes (30, 31) that these can be further oxidized to acids:



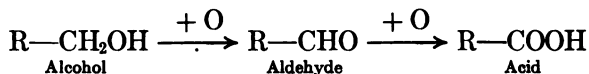
The group  $-\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$  is called carboxyl. Its  $-\text{OH}$  complex behaves like a unit in the reaction of a carboxyl with the chlorides of phosphorus, the resulting compounds being *acid chlorides*:



In water solution the organic acids give the tests characteristic of the hydrogen ion, *i.e.* they are acid in taste and redden blue litmus, and change the color of numerous dyes from that seen in their alkaline solutions. The compounds containing the carboxyl group conduct the electric current as do the inorganic acids, but frequently to a much less extent, since many of them are to be classed among the weak acids, *i.e.* they dissociate the hydrogen ion to but a slight extent.

For each of the primary alcohols there is a corresponding aldehyde and acid, thus:

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The acids derived from the aliphatic hydrocarbons are called fatty acids because most of them are found as esters in the fats of animals and plants. The lower members of the series are liquids of pungent odor and corrosive action. They boil without decomposition and are readily soluble in water and behave like strong acids.

**Formic acid**,  $\text{HCOOH}$ , is the lowest member of the series. It occurs free in ants and in the stings of some insects, as bees and caterpillars, and also in certain nettles, in the fruit of the soap tree (*Sapindus saponaria*), and in tamarinds and fir cones. It is always found in traces in perspiration and in urine. It is a colorless liquid with a pungent odor. At  $20^\circ$  its specific gravity is 1.221. It solidifies in a freezing mixture, melts at  $+8.3^\circ$  and boils at  $100.8^\circ$ . Formic acid is readily soluble in water and in many organic solvents. Its vapors are combustible.

It is the strongest acid of the series, being dissociated into  $\text{H}^+$  ions to about twelve times the extent of acetic acid. It produces intense irritation of the skin and forms blisters.

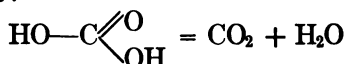
**Formic acid** does not behave like its homologues in certain respects. It is easily oxidized, with the formation of carbon dioxide and water, and therefore possesses strong reducing power, depositing mercury and silver from solutions of their oxides. In this respect it has the properties of an aldehyde, and its ready decomposition through oxida-

tion probably finds its explanation in the acid possessing

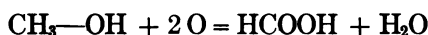
the formula  $\text{HO}-\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{H} \end{smallmatrix}$ , or hydroxy formaldehyde.

On taking up oxygen the compound, hydroxy formic acid containing two hydroxyls,  $\text{HO}-\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$ , is formed.

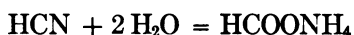
Two hydroxyls cannot remain attached to a single carbon atom, however, except in a few circumstances (see chloral), and water is immediately separated with the liberation of carbon dioxide:



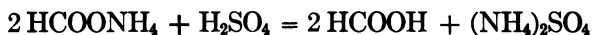
*Formation.* — (1) Formic acid is obtained by the oxidation of methyl alcohol:



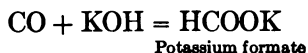
(2) Hydrocyanic acid, HCN, behaves as a nitrile in that it can take up two molecules of water, forming the ammonium salt of formic acid:



From the ammonium salt free formic acid can be obtained by treatment with a nonvolatile acid and distilling:

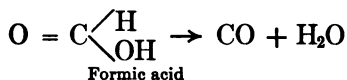


(3) Carbon monoxide gas, CO, reacts with the caustic alkalies:



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*Chemical behavior.* — (1) The above reaction serves as another example of the passage of carbon from the divalent to the tetravalent state (40). At 169° formic acid is again dissociated into water and carbon monoxide:

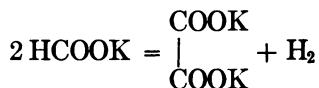


indicating that at high temperatures the carbon in certain complexes tends to become spontaneously divalent.

(2) On strongly heating the alkali formates with alkali hydroxide they are decomposed into alkali carbonate and hydrogen:

$$\text{HCOOK} + \text{KOH} = \text{K}_2\text{CO}_3 + \text{H}_2$$

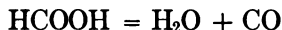
(3) The alkali formates when heated to about 400° decompose into oxalic acid and hydrogen:



(4) Formic acid can be transformed back into its nitrile, HCN, by heating its ammonium salt above its melting point. As an intermediary product, formamide (53), is produced:



(5) Concentrated sulphuric acid withdraws the elements of water from formic acid, liberating carbon monoxide:



Of the salts of formic acid most are readily soluble. Mercury formate,  $(\text{HCOO})_2\text{Hg}$ , and silver formates,

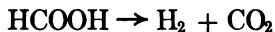
Ag(HCOO), are difficultly soluble, but are readily decomposed on warming. Lead formate, Pb(HCOO)<sub>2</sub>, is soluble in 63 parts of water at 16° and in 5.5 parts at 100°. Zinc formate, Zn(HCOO)<sub>2</sub>, is insoluble in alcohol, a property which distinguishes it from the zinc salts of its volatile homologues, acetic, butyric, etc.

(6) The reduction of the heavy metals by formic acid may be illustrated by the decomposition of the silver and mercuric salts :



(7) A qualitative test for formic acid which is of great delicacy rests on the formation of carbon monoxide gas on heating with concentrated sulphuric acid. The gas is passed into a dilute solution of blood and the latter is then examined spectroscopically for the characteristic spectrum of carbon monoxide hæmoglobin.

(8) A property of formic acid of great interest biologically is that of spontaneously decomposing into hydrogen and carbon dioxide in the presence of metallic rhodium :

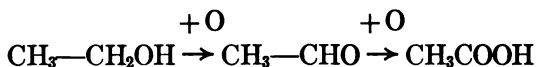


The attempt has been made to explain the mechanism of fermentation on the assumption that yeast produces an organic catalyst which effects this decomposition (see Fermentation, 164).

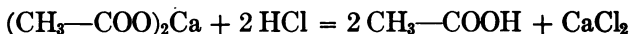
**51. Acetic acid**, CH<sub>3</sub>COOH, is the acid found in vinegar, where it is derived by the fermentation of glucose

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into alcohol and the subsequent oxidation of the alcohol through aldehyde to acid :



Its formation is the cause of the souring of beer, wine, and cider. Cider vinegar contains small amounts of alcohol and of acids other than acetic (tartaric, succinic, etc.) and also ethyl esters of these acids, and to these it owes its flavor. It contains usually but 3 to 5 % of acid. The acid volatilizes readily, and in order to obtain it in a pure form from its dilute solutions it is converted into a salt which, being non-volatile, can be heated to evaporate the water. The salt is finally treated with hydrochloric acid, avoiding an excess, and the mixture distilled, when strong acetic acid passes over :



*Pyroligneous Acid.* — When hardwoods are heated in a distilling apparatus, a tarry product containing carbolic acid and related substances is formed, and there distills over a gaseous mixture containing hydrogen, methane, carbon monoxide, and carbon dioxide, a moderate amount of higher hydrocarbons (7 %), and a mixture of water, methyl alcohol, acetone, and acetic acid, together with numerous other compounds in small quantities as impurities. This mixture is known as *pyroligneous acid*. Methyl alcohol and acetone are so readily volatile that they can be distilled from the dilute acetic acid, thus effect-

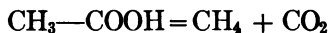
ing a partial separation. The acetic acid is then neutralized with lime, forming calcium acetate,  $\text{Ca}(\text{OOC}-\text{CH}_3)_2$ , and the latter is then heated to  $200^\circ$  in contact with air to oxidize the tarry matters. From this crude calcium acetate the acetic acid is obtained.

In marked contrast to formic acid, acetic acid is extraordinarily resistant to oxidation. It is not oxidized by chromic acid under any ordinary conditions and can be passed through a glowing tube without decomposition. It is not oxidized by dilute solutions of potassium permanganate, which quickly decompose formic acid. Silver acetate in water solution can be heated without reduction (blackening) taking place.

It is this great stability which explains why acetic acid occurs in such large quantities in the pyrolygneous acid. During the decomposition of the various complex compounds (cellulose, lignin, pentosans, etc.) numerous decomposition products are formed which, being unstable at high temperatures, are further decomposed, and in the end only the most stable products remain. Numerous compounds on oxidation yield acetic acid, and owing to its great stability the reaction stops at this point.

Even the animal body possesses but a very limited capacity to oxidize acetic acid. Normal human urine contains from 60 to 280 mgm. of acetic acid per day.

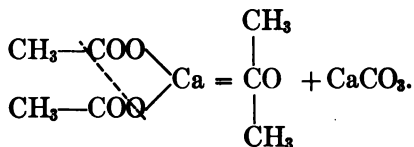
Acetic acid, despite its stability, is readily fermented in the form of its calcium salt by certain organisms into methane and carbon dioxide:



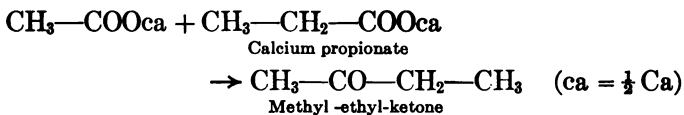


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Calcium acetate when heated in the dry condition to the point of decomposition yields acetone and calcium carbonate:



This type of decomposition is common to the higher fatty acids and is therefore a general method of preparing ketones. When the salts of two different acids are employed, mixed ketones result:



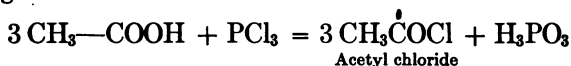
*Glacial Acetic Acid.*—When nearly free from water acetic acid solidifies when cooled below 16.7° to a crystalline mass, from which it derived its name, *glacial acetic acid*. It boils at 118° and has a specific gravity of 1.055 at 15°. When mixed with water, contraction and increase in density ensue, the maximum change taking place when equal molecules of water and acetic acid are combined. This solution contains 76 per cent acid and at 15° has a specific gravity of 1.075. On further dilution the specific gravity decreases until a 50 per cent solution has nearly the same density as has the glacial acid. It is therefore impossible to employ the specific gravity as an index to the strength of this acid. This is obtained by titration with a standard solution of an alkali employing an indicator.

*Tests for acetic acid:* (1) The odor of acetic acid is extraordinarily characteristic and easily recognizable.

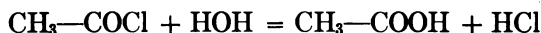
(2) When acetic acid or an acetate is treated with alcohol and sulphuric acid, the characteristic odor of ethyl acetate is obtained.

(3) From concentrated solutions silver nitrate precipitates the white, difficultly soluble silver acetate, which contains 64.65 per cent of silver.

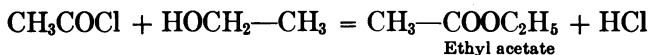
**52. The Acid Chlorides.** — The fatty acids are acted upon by the trichloride of phosphorus with the replacement of hydroxyl by chlorine, the resulting compounds being known as *acid chlorides*:



It is a liquid with a suffocating odor, which boils at 51°, specific gravity 1.138 at 0°. It fumes in the air owing to its reaction with the moisture therein. It decomposes violently with water, forming acetic and hydrochloric acids:



With alcohols it reacts to form esters:

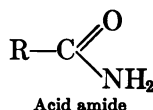
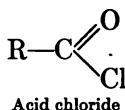
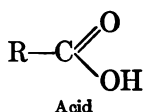


This reaction is one of great importance in determining the presence and number of hydroxyl groups which are contained in a compound under investigation. The ester is produced according to the above reaction. This is a neutral compound and can be separated from the excess of acetyl chloride by treatment with water. A measured quantity of the acetyl compound (ester) is then treated

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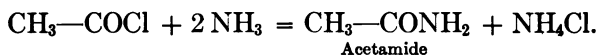
with a known volume of standardized alcoholic potassium hydroxide and heated until the ester is completely hydrolysed, *i.e.* reconverted into acetic acid and alcohol. From the amount of alkali used up in neutralizing the acetic acid which was formed in the hydrolysis the number of hydroxyl groups can be estimated.

**53. The Acid Amides.** — The amides may be regarded as organic acids in which the hydroxyl of the carboxyl group is replaced by the amino group,  $-\text{NH}_2$ :

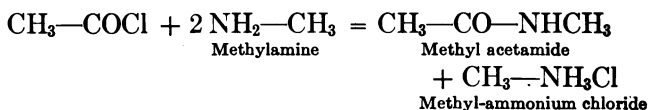


The amides are formed in several ways which illustrate their relationship to other classes of compounds:

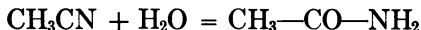
(1) Acid chlorides react with ammonia, forming hydrochloric acid and amide:



If substituted ammonias (amines) are employed for ammonia, alkylated amides result:



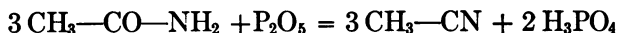
(2) The alkyl nitriles react with one molecule of water, forming acid amides:



This reaction is the first step in the formation of acid from nitrile. The amides take on a second molecule of

water, passing into the ammonium salts of the corresponding acids (50).

Strong dehydrating reagents, such as phosphorus pentoxide, can abstract from the acid amides a molecule of water with the regeneration of nitriles:

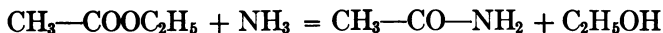


In order to effect the addition of one molecule of water only, the nitriles are treated with some reagent which contains water, but which has a strong affinity for the latter (*e.g.* strong sulphuric or hydrochloric acid).

(3) By the dry distillation of the ammonium salts of the fatty acids, or by heating them in a closed tube to  $230^\circ$ , water is separated with the formation of the amide:



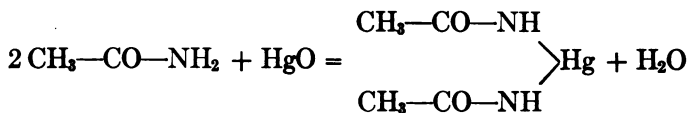
(4) Esters can react with ammonia with the production of amides and alcohols:



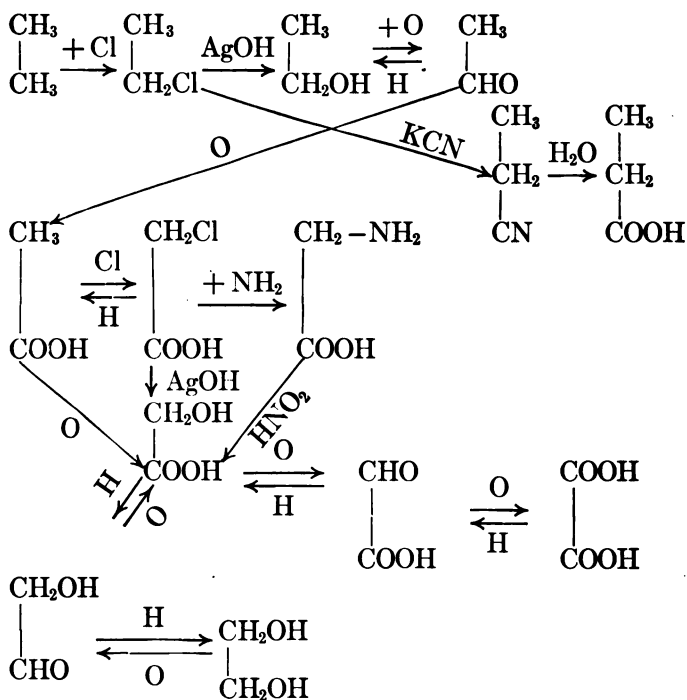
The amides, being derivatives of ammonia, which is strongly basic, formed by the exchange of one hydrogen for an acid radical, possess very feeble basic properties. Thus acetamide forms a salt with hydrochloric acid, which is however very easily decomposed by water. Acetamide hydrochloride is formed when dry hydrochloric acid gas is passed into an ethereal solution of acetamide.

On the other hand the hydrogen of the  $\text{NH}_2$  group in the acid amides behaves like acid hydrogen. An aqueous solution of acetamide dissolves mercuric oxide, forming a compound analogous to the salts:

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The relationships and mutual transformations among the compounds of the types thus far considered, excluding the ethers and esters, are shown by the following scheme. The series includes some compounds which will be considered immediately :



**54. Halogen Derivatives of Acetic Acid.**—When chlorine or bromine acts upon acetic acid a substitution of hydrogen by halogen takes place. The resulting products may be mono-, di-, or trichloroacetic acid depending on the extent of the substitution.

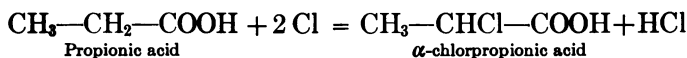
Chloroacetic acid,  $\text{CH}_2\text{Cl}-\text{COOH}$ , melts at  $62.5^\circ$ . It exerts a corrosive action similar to that of glacial acetic acid on the skin, and the vapors are highly irritating.

Dichloroacetic acid,  $\text{CHCl}_2-\text{COOH}$ , melts at  $-4^\circ$ . Its chief interest is its usefulness in syntheses of other compounds.

Trichloroacetic acid,  $\text{CCl}_3-\text{COOH}$ , is a solid, M. P.  $80^\circ$ . It is extremely caustic in its action on the skin, and is employed for the removal of warts, corns, and similar growths. It is likewise employed as a precipitant for proteins, with which it forms compounds which are relatively insoluble in water or dilute acids.

The acidity of the chlorinated acetic acids, *i.e.* the degree of dissociation of hydrogen ions, increases with increasing chlorine. All are stronger acids than acetic. The strength of trichloroacetic acid ranks it with the strong mineral acids.

With fatty acids containing three or more carbon atoms chlorine or bromine react to form halogen substituted acids. In all cases the hydrogen substituted is one bound to the carbon atom neighboring the carboxyl group. This is designated the *alpha* carbon atom and is usually abbreviated *a*. Thus:

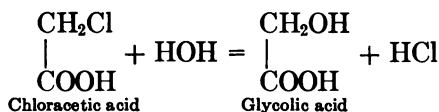


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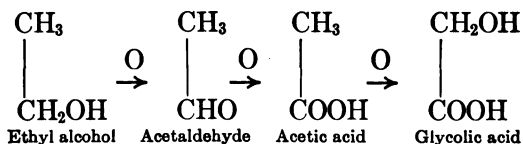
The successive carbon atoms of the fatty acids are designated by the letters of the Greek alphabet, in order of their position, with respect to the carboxyl group.

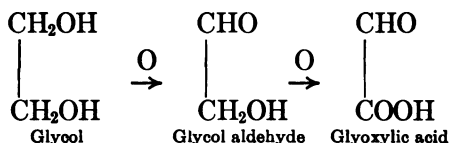
Thus:  $\dots \underset{\delta}{\text{CH}_2} - \underset{\gamma}{\text{CH}_2} - \underset{\beta}{\text{CH}_2} - \underset{\alpha}{\text{CH}_2} - \text{COOH}$

**55. The Hydroxy Acids.** — With water on prolonged boiling the alpha-halogen acids react with the replacement of halogen by hydroxyl. The exchange is greatly facilitated by the presence of silver oxide.



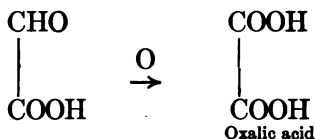
Glycolic acid is of interest from the biological standpoint. It may be regarded as an oxyacetic acid. It is found in unripe grapes, in sugar cane, and in many other plants, especially in the green parts. It is taken internally therefore with the food to a slight extent. It is somewhat toxic in large doses. It is a crystalline compound, M. P. 80°, easily soluble in water, alcohol, and ether, but difficultly in acetone. It does not appear in the urine after administration, but has been found after the ingestion of glycol. It is a possible intermediary product of the oxidation of certain complex foodstuffs in the course of metabolism. Its relation to alcohol and glycol, from which it is formed by oxidation, is seen from the following formulæ:



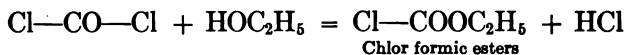


On further oxidation it yields a compound called glyoxylic acid, which is at the same time both an acid and an aldehyde.

Glyoxylic acid is in turn in conformity with its aldehyde nature oxidized to *oxalic acid* (100) which contains two carboxyl groups:



**56. The Amino Acids.** — Not only can a hydrogen atom of the methyl group of acetic acid be replaced by halogen, hydroxyl, or alkyl group, but also by the amino group  $\text{—NH}_2$ , with the formation of *amino acids*. In respect to halogen, hydroxyl, and amino derivatives, formic acid behaves very differently from its homologues, acetic, propionic, etc., acids. Thus chlor formic acid  $\text{ClCOOH}$  is incapable of existence in the free state, but its esters are known. Thus  $\text{COCl}_2$ , which is to be regarded as the acid chloride of chlor formic acid, reacts with alcohols to form chlor formic esters:

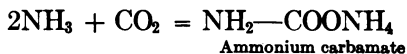


The chlor formic esters behave like acid chlorides, however, in that they are decomposed by water.

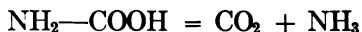
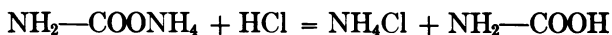


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*Carbamic Acid.*—The ammonium salt of amino-formic acid, or *carbamic acid*, is formed when ammonia gas reacts with carbon dioxide:



Ammonium carbamate is present as an impurity in commercial ammonium carbonate. On treatment of  $\text{NH}_2\text{—COONH}_4$  with a mineral acid it is at once decomposed with evolution of carbon dioxide:

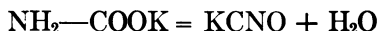


The metallic salts of carbamic acid are more stable, but decompose at ordinary temperatures in solution into carbonates:



Carbamic acid is distinguished from carbonic acid in the solubility of certain of its salts. Solutions of sodium or potassium carbamate give no precipitate with calcium chloride, as do the corresponding carbonates.

The alkali salts of carbamic acid lose water on heating to redness and pass into the cyanates:

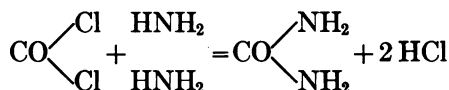


Ammonium carbamate is an intermediary compound in the formation of urea in the living tissues. Ammonium carbamate on the abstraction of a molecule of water forms the amide of carbamic acid, or *carbamide*, the popular name for the latter being *urea*, a name which was given to the

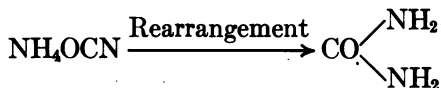
principal nitrogenous compound in the urine of mammals before the development of the science of organic chemistry:



This structure of urea is further confirmed by its formation from carbon oxychloride and ammonia:



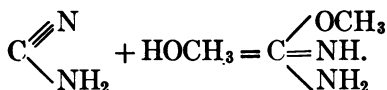
Urea is likewise produced by a rearrangement of the atoms within the molecule of ammonium isocyanate when the latter is heated above its melting point:



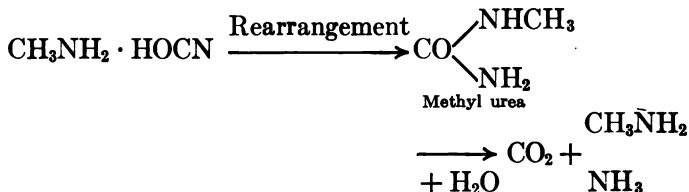
This transformation was observed by Wöhler in 1828 and was the first synthesis of an organic compound. The change of ammonium isocyanate into urea is never quite complete, for a condition is reached where a definite proportion between the isocyanate molecules and urea molecules exists. The reaction is reversible. When silver nitrate is added to a solution of pure urea, silver isocyanate is precipitated. The amount of isocyanate present in such solutions is, however, extremely small, but if removed by the formation of an insoluble compound the reaction proceeds in the direction which leads to its formation. In certain reactions urea behaves as if it had the struc-

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ture  $\text{C} \begin{array}{l} \text{NH} \\ \diagup \\ \text{OH} \\ \diagdown \\ \text{NH}_2 \end{array}$ . Thus methyl alcohol condenses with cyanamid  $\text{C} \begin{array}{l} \text{N} \\ \diagup \\ \text{NH}_2 \end{array}$  to form *methyl isourea*:

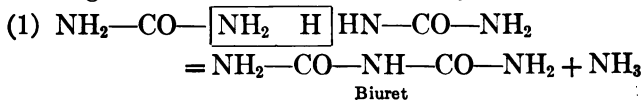


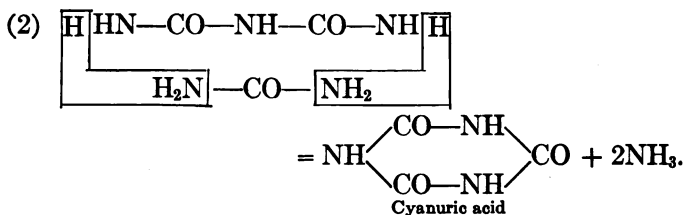
The structure is proven by the fact that on heating this compound with hydrochloric acid (hydrolysis) methyl chloride is formed. From *methylurea*, which is formed when the salt of cyanic acid with methylamine (methyl ammonium cyanate) is heated alone, there results, on hydrolysis with hydrochloric acid, methylamine:



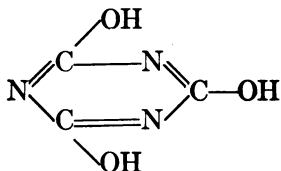
In isomethyl urea the methyl group cannot be linked to nitrogen.

When heated, urea melts and at a higher temperature begins to evolve gas, consisting of ammonia and carbon dioxide. The melt finally solidifies. There are several types of decomposition which take place, the principal ones being the formation of *biuret* and cyanuric acid.





The reactive form of cyanuric acid is probably not that indicated by the above formula. It is a tribasic acid, and forms salts, indicating the presence of three acid hydrogens. It is best represented by the following structural formula:

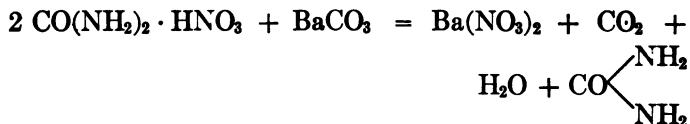


**57. Urea** is one of the longest known of organic compounds. It constitutes 85–90 % of the nitrogen of normal human urine. The average amount of urea eliminated daily by a man on an ordinary diet is about 30 grams. The amount may vary greatly with the character of the diet, being high when much protein is eaten and low when the protein intake is low. It is a neutral substance, forming crystals which melt at 130–132°; very soluble in water (1 : 1) and in alcohol (1 : 5 of cold alcohol), but insoluble in ether and chloroform.

Urea is a neutral substance with respect to indicators, but acts as a feeble base in that it forms salts with acids. Urea nitrate,  $\text{CO}(\text{NH}_2)_2 \cdot \text{HNO}_3$ , is a crystalline compound soluble in water, but slightly soluble in nitric acid. It is

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slightly soluble in alcohol, but easily in acetone. It is employed for the isolation of urea from urine. The salt is decomposed by barium carbonate :



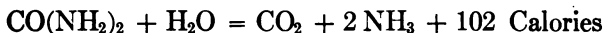
The urea is separated from  $\text{Ba}(\text{NO}_3)_2$  by solution in alcohol. Urea forms salts with other acids, the most important being that with oxalic acid,  $[\text{CO}(\text{NH}_2)_2]_2\text{C}_2\text{H}_2\text{O}_4$ . This is a crystalline compound soluble in water, but nearly insoluble in oxalic acid solutions, slightly soluble in alcohol. It is also employed for the isolation of urea from urine.

Urea also forms a compound with mercuric nitrate and mercuric oxide of the formula :



It likewise forms a compound with mercuric oxide,  $\text{CO}(\text{NH}_2)_2\text{HgO}$ .

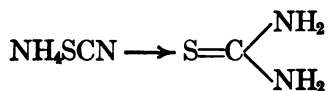
Urea in moderate concentration possesses no appreciable toxicity for the higher animals, but is much more toxic to birds. The latter do not excrete their waste nitrogen as urea, but principally as ammonium urate (147). Even in so great dilution as  $\frac{1}{4}\%$  solutions, urea is noticeably toxic to certain plants. Certain bacteria can employ urea as a source of energy, although it yields very little energy on decomposition. The change which takes place in urea fermentation is as follows :



Since the fermentation always takes place in solution, the products of the decomposition unite with water to form ammonium carbonate. This decomposition of urea is brought about by an enzyme or organic catalyzer produced by the microorganisms. It has recently been discovered that this enzyme, which is called *urease*, is present in liberal amounts in certain beans, notably the Jack bean and the Soy bean. When an extract of the beans is added to a solution of urea and the mixture protected from bacterial action by toluene, the transformation of urea into ammonium carbonate takes place rapidly and is complete within a few hours at favorable temperatures. The ammonia is titrated, employing methyl orange as indicator, either directly or after aspirating it into a solution of standard acid. This method was first described by Marshall.

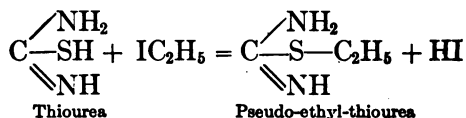
The quantitative estimation of urea by the Folin-Benedict method is effected by converting it into  $\text{CO}_2$  and  $\text{NH}_3$  by heating the acidified urine in an autoclave. The resulting ammonia is removed by a current of air and is absorbed by a measured quantity of standard acid. A separate determination of ammonia is made on an unheated sample and the result subtracted from that obtained with the heated, the difference representing urea.

**58.** Thiourea is formed from ammonium isothiocyanate on treating in a manner analogous to the formation of urea from ammonium isocyanate :

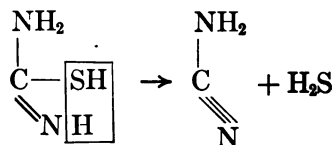


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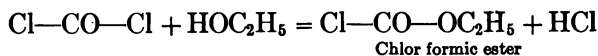
Thiourea crystallizes readily in very large crystals. It is readily soluble in water but insoluble in alcohol. It melts at  $172^{\circ}$ . It exhibits the behavior of existing in the tautomeric form in part, for on treatment with alkyl iodide it forms alkyl thioureas which possess the *pseudo* form, the alkyl group being linked to sulphur instead of nitrogen:



That the alkyl group is linked to sulphur is shown by its decomposition into ethyl mercaptan instead of ethyl amine, as it would were the ethyl group linked to nitrogen (57). When treated with mercuric oxide thiourea loses hydrogen sulphide and forms cyanamide:

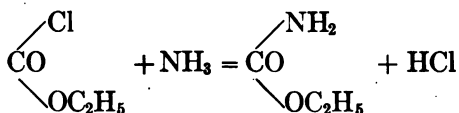


**59. Esters of Carbamic Acid.**—Carbon oxychloride,  $\text{COCl}_2$ , which is formed by the direct union of carbon monoxide and chlorine in sunlight, can react with alcohol to form the ethyl ester of chlor formic acid:



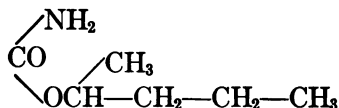
Chlor formic ethyl ester is a volatile liquid of very pungent odor which boils at  $93^{\circ}$ . It reacts like an acid chloride, being decomposed by water.

60. **Urethanes.** — Chlor formic ester reacts with ammonia to form *amino ethyl formate*, the ethyl ester of amino formic acid. This compound is called *urethane*:



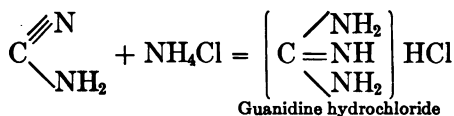
Urethane is a colorless crystalline substance possessing a faint peculiar odor and a taste somewhat like that of potassium nitrate. It is soluble in 0.6 parts of alcohol, 1 part of water, 1 part of ether, and in 3 parts of glycerol. It melts at 48–50° and boils at 180°. It is employed as a sedative and hypnotic. A number of derivatives of urethane have been introduced as hypnotics and sedatives in the quest for those which possess the most advantageous properties. Among these may be mentioned:

*Hedonal* is an ester of carbamic acid with the amyl alcohol, methyl propyl carbinol:



It has a greater hypnotic effect than has urethane. The urethanes are diuretics, as well as hypnotics. In the body they are oxidized to carbon dioxide and urea.

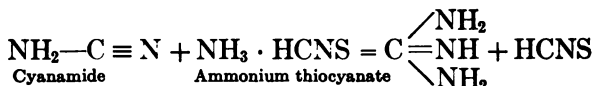
61. **Guanidine** is formed when cyanamide reacts with ammonium chloride:





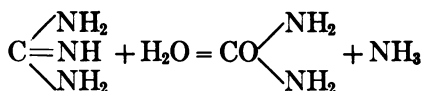
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It may be regarded as urea in which the oxygen is replaced by the divalent =NH group (imino group). It also results from heating thiourea through the loss of hydrogen sulphide :

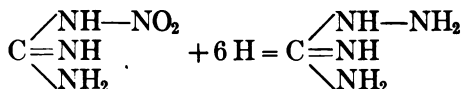


Guanidine is a colorless crystalline compound of a strongly basic character which absorbs moisture and carbon dioxide readily, forming a solution of guanidine carbonate,  $[\text{NH}=\text{C}=(\text{NH}_2)_2]\text{HCO}_3$ .

It is hydrolyzed by alkalies to urea and ammonia :



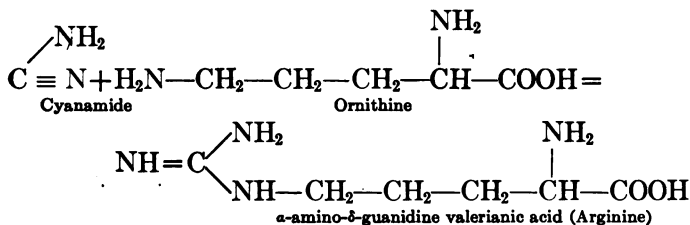
Guanidine reacts with strong nitric acid to form a nitro compound, *nitro guanidine*, which on reduction yields *amino guanidine* :



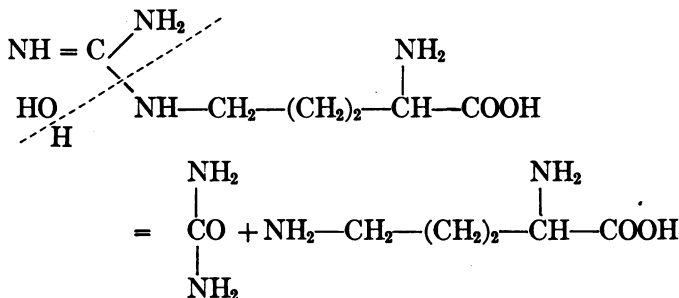
The latter is hydrolyzed by boiling with dilute acids or alkalies, forming hydrazine (32), carbon dioxide, and ammonia.

**62. Arginine** is an amino acid obtained by the hydrolysis of proteins by mineral acids. On hydrolysis by alkalies it is split up into urea and *ornithine*, an acid con-

taining five carbon atoms and two amino groups, which is known by its behavior and synthesis to be  $\alpha$ - $\delta$ -diamino valerianic acid (71). Furthermore arginine is synthesized by the condensation of cyanamide and ornithine :



Its cleavage into urea and ornithine is illustrated by the reaction :

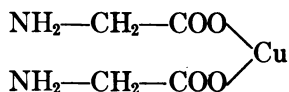


On vigorous treatment with alkalis the urea passes on into ammonia and carbon dioxide (57).

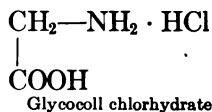
Arginine is a white crystalline compound which melts at  $207.5^\circ$  with decomposition. It is easily soluble in water, but insoluble in alcohol. It is precipitated by phosphotungstic acid, and by silver nitrate in the presence of barium hydroxide.

63. Aminoacetic Acid, glycine, glycocoll,  $\begin{array}{c} \diagup \text{NH}_2 \\ \text{CH}_2 - \text{COOH} \end{array}$ , is found in the free state in the adductor muscle of the scallop and in plant juices. It is a constituent of many proteins and is formed from these on hydrolysis by acids. It is the only amino acid derived from proteins which is certainly dispensable from the diet during growth. It plays an important rôle in the body as a protective substance, being condensed with several types of organic acids which are toxic, forming, with the separation of water, combinations which are of very much lower toxicity. An example of such a union is hippuric acid (see Hippuric Acid). Glycocoll is also a constituent of bile, where it exists combined with cholic acid as glycocholic acid.

Glycocoll is both an acid and base by reason of its carboxyl and amino groups, but these neutralize each other's effects so that its solutions react neutral to litmus, phenolphthalein, and certain other indicators. It forms salts with bases, the most important because of its tendency to crystallize being that with copper:



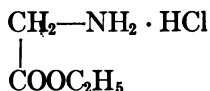
This salt forms a deep blue solution. It likewise forms salts with acids, *e.g.* :



These salts are crystalline, but are extremely soluble in water and are acid in reaction.

Of great importance in the isolation of glycocoll, as well as other amino acids, is the ethyl ester. It is formed by passing dry HCl gas into a suspension of the amino acid in absolute alcohol. As the hydrochloride is formed, it goes into solution and is then esterified. When the alcohol is evaporated the hydrochloride of the ester is obtained. From this, on treatment with strong sodium hydroxide, the ester is set free from the HCl and can be extracted with ether. All the esters of the amino acids are soluble in ether.

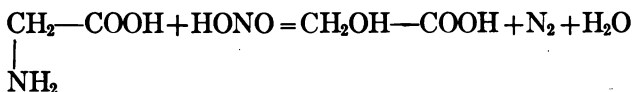
Glycocoll ester chlorhydrate is very sparingly soluble in



absolute alcohol, which contains all the HCl gas which it can dissolve and crystallizes from such a solution to an extent approximating a quantitative separation. This principle has been utilized for its estimation and preparation.

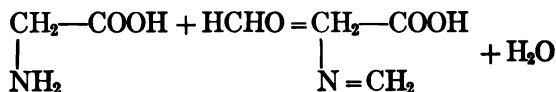
Glycocoll ester distills with some decomposition at ordinary pressures at 150°. Under diminished pressure it distills without decomposition.

With HNO<sub>2</sub> glycocoll, like other amino acids, decomposes with the formation of a hydroxy acid and elementary nitrogen.

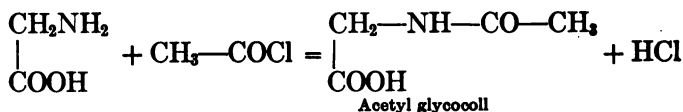


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With formaldehyde its amino group condenses to form a methylene derivative which has no basic properties and can be sharply titrated with alkali and an indicator:

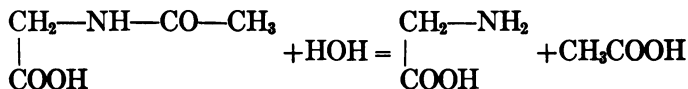


Amino acids, when treated with acid chlorides, yield *acetyl* derivatives of the following type:



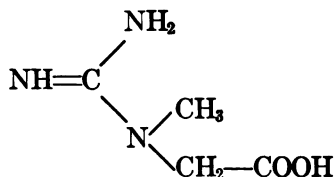
Acetyl derivatives of the amines and amino acids are readily hydrolyzed into acetic acid and free amino group by boiling with dilute alkalis. Derivatives of this class can be formed by employing chlorides of other organic acids, as propionyl or butyryl chlorides. The groups are collectively known as *acyl* radicals, and the process of forming esters from alcohols and acid chlorides or amides from amines and acid chlorides is known as acylation.

Acyl derivatives can frequently be purified much more satisfactorily, because of greater insolubility or greater tendency toward crystallization, than the alcohols or amines themselves, and are useful for the isolation and purification of many compounds, these being afterward regenerated by hydrolysis:



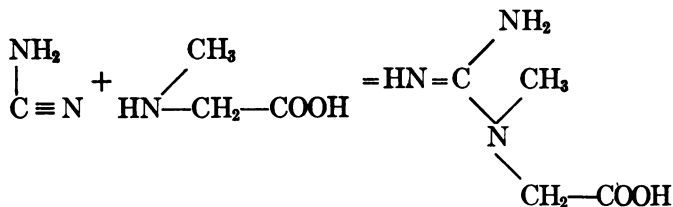
Of special value in the isolation and purification of various amino acids are the compounds analogous to the acyl derivatives, obtained from certain aromatic acids.

**Creatine**, methyl-guanidine acetic acid,



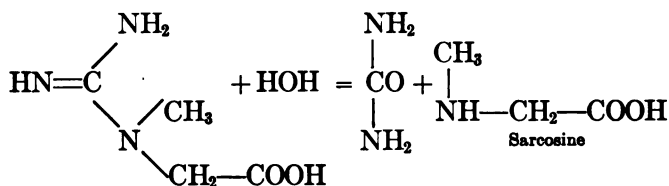
is found in muscle and organ tissues of vertebrates, but is not found in invertebrates. It is remarkably constant in amount, being found in human muscle to the extent of .39 per cent, and .52 per cent and .45 per cent respectively in the muscle of the rabbit and cat. It is not found in normal urine, but appears when carbohydrates are absent from the diet. It is not known how creatine is formed in the body.

Creatine is a colorless crystalline compound with a bitter taste, which contains one molecule of water of crystallization which it loses at 100°. It is a base and forms salts with acids. It is formed synthetically by the condensation of cyanamide with methyl-amino acetic acid:

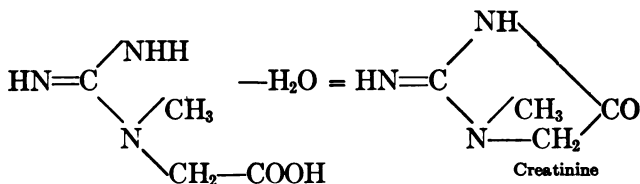


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It is soluble in 74.4 parts of water at 10°; 100 cc. of 85 per cent alcohol at 17° dissolve .008 grams. On heating with alkalis it is hydrolyzed into urea and sarcosine or *methyl glycocoll*.

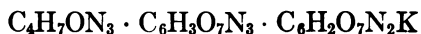


**Creatinine** is the *inner anhydride* of creatine. It is formed from creatine by boiling with mineral acids, which causes the abstraction of the elements of water:



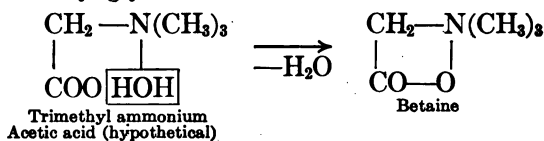
This compound is a never failing constituent of the urines of mammals. The daily excretion for man is .75 to 1.5 gram, and on diets free from creatine or creatinine the output is surprisingly constant and is independent of the intake of protein. Its precursor in the body is unknown.

Creatinine is soluble in 11.5 parts of cold water and more readily in hot. It dissolves in 625 parts of cold absolute alcohol. It is a stronger base than ammonia and displaces the latter from its salts. The most important salts are the potassium creatinine picrate,

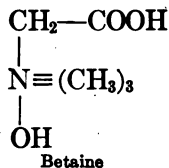
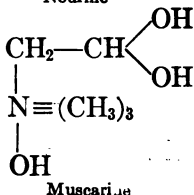
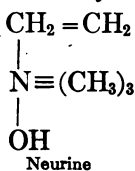
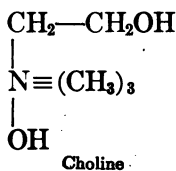
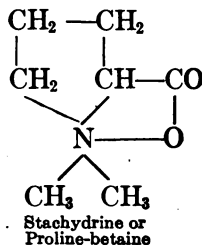
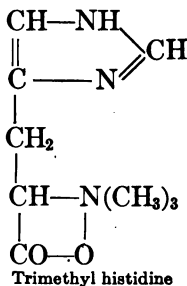
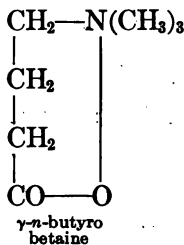


and the zinc chloride double salt,  $(C_4H_7ON_3)_2ZnCl_2$ . The most important color reaction of creatinine is that with picric acid and sodium hydrate. The color closely resembles the deep orange of a solution of potassium dichromate.

**The Betaines.**—These form a group of natural bases. The simplest member of the group is *betaine* or trimethyl glycocoll.



Its relation to the following bases is of interest :



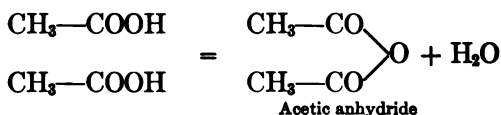


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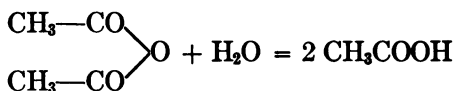
The betaines are found in numerous plant extracts. Those from mushrooms and spores have been most investigated.

*γ-n-butyro betaine* has been isolated from putrid meat; *trimethyl histidine* and *muscarine* from mushroom extract; *stachydrine* from various plants; and *choline* and *neurine* from the brain, the latter only after decomposition.

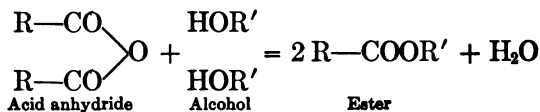
**64. Acid Anhydrides.**—There exists an important class of compounds which may be regarded as derived from two molecules of acid by the abstraction of a molecule of water. These are known as acid anhydrides:



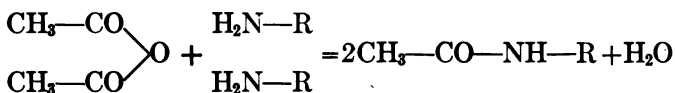
Corresponding anhydrides of the other fatty acids are known. The lower members are liquids; those of higher molecular weight, solids of neutral reaction. The lower members react readily with water, regenerating the acids from which they were formed:



The higher members are much more stable toward water. Acid anhydrides react with alcohol to form esters in the sense of the following equation:

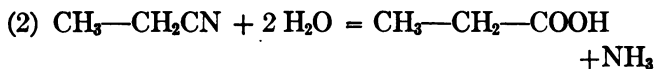
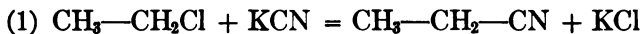


They are therefore useful in the same way as are the acyl chlorides for acylating alcohols. With primary and secondary amines they react, producing acyl derivatives :

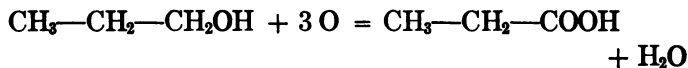


*Acetic anhydride*,  $(\text{CH}_3\text{—CO})_2\text{O}$ , is the most important of the anhydrides of the fatty acids. It is a mobile liquid of suffocating odor, B.P.  $137^\circ$ , Sp. Gr. 1.073 at  $20^\circ$ . It is a reagent of great importance, being employed for the production of acyl derivatives.

**65. Propionic Acid**,  $\text{CH}_3\text{—CH}_2\text{—COOH}$ , the next homologue of acetic acid, is found in sweat and in mixtures resulting from the putrefaction of proteins by bacteria, where it is derived from certain amino acids by reactions which will be described later. It is formed from ethyl chloride through propionitrile, as an intermediate product :



It is likewise formed by the oxidation of primary propyl alcohol :

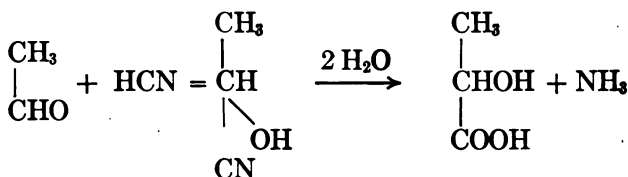


This mode of formation makes clear its structure. It is a liquid with an odor which is suggestive of acetic acid, but is easily distinguishable from it. B.P.  $140.7^\circ$ . It is soluble in water in all proportions, but much less so in

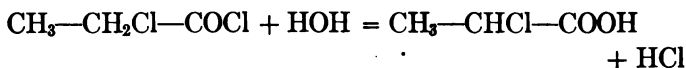
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strong calcium chloride solutions. On adding this salt to its solutions it separates as an oil. Propionic acid is difficult to test for with certainty, since its properties are so closely similar to those of its immediate homologues, acetic and butyric acids. The silver salt contains 59.65 % of silver, and the barium salt 48.40 % of barium. The analysis of these salts, both of which are sparingly soluble in water, is the most convincing qualitative test.

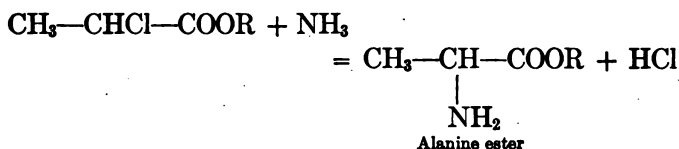
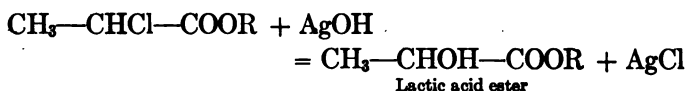
$\alpha$ -chlor propionic acid,  $\text{CH}_3\text{—CHCl—COOH}$ , is formed by the direct action of chlorine upon propionic acid in the sunlight. The isomeric  $\beta$ -chlor derivative,  $\text{CH}_2\text{Cl—CH}_2\text{—COOH}$ , is likewise formed to some extent. The structure of these acids is made clear by other methods of formation; thus acetaldehyde adds hydrocyanic acid, forming hydroxy propionitrile:



$\alpha$ -hydroxy propionic acid, or lactic acid, yields when treated with  $\text{PCl}_5$  a product in which both the hydroxyl group of the carboxyl and that on the  $\alpha$ -carbon atom are replaced by chlorine, viz.:  $\alpha$ -chlor propionyl chloride,  $\text{CH}_3\text{—CHCl—COCl}$ . This, like acid chlorides in general, is decomposed by water, forming  $\alpha$ -chlor propionic acid:



$\alpha$ -chlor propionic acid is of interest because it can be employed either for conversion into lactic acid or into  $\alpha$ -amino-propionic acid, or alanine, one of the amino acids derived from proteins on hydrolysis:



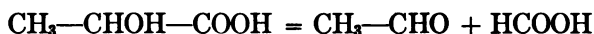
66. **Lactic Acid**,  $\text{CH}_3\text{—CHOH—COOH}$ , is the acid of sour milk. It is formed from milk sugar by the action of the lactic acid bacteria. Other sugars, as cane sugar, can likewise be used by this organism with the production of this acid. If a liter of 10 % cane sugar solution be treated with 40 grams of calcium carbonate and 20-30 cc. of sour milk to supply the bacteria and the proteins, salts, etc., necessary for their multiplication, and the mixture kept at 37° for six to eight days, with occasional agitation, it will contain a considerable amount of calcium lactate. The solution is then boiled and evaporated to a small volume and cooled, when calcium lactate will crystallize out. On treating the crystals with sulphuric acid, calcium sulphate and free lactic acid are formed. The lactic acid can be extracted from the mixture by ether, in which it is readily soluble. On distilling off the ether lactic acid remains.

Lactic acid occurs in other fermented substances, such as

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sauerkraut and ensilage, in both cases arising through the agency of microorganisms. The conditions essential to the preservation of succulent vegetables and green fodders in these forms are close packing in an air-tight container from which the gases produced can escape. Rapid fermentation and respiration quickly remove the small amount of oxygen from the container, and through the catalytic action of enzymes in the plant cells a part of the sugars are converted into lactic acid. The acidity, together with the very considerable rise in temperature, causes the death of most of the microorganisms, and the material is preserved from putrefaction or further fermentation.

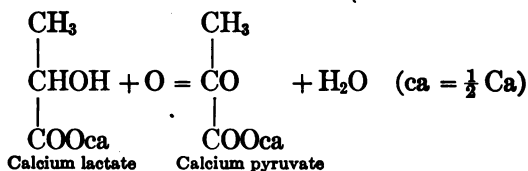
Lactic acid is a sirupy liquid which decomposes on distillation at ordinary atmospheric pressure, but can be distilled at about  $85^{\circ}$  if the pressure be reduced to .5 mm. of mercury. Distilled in this way, it crystallizes. The crystals are hygroscopic. It is readily soluble in water, alcohol, and ether, but insoluble in chloroform, carbon disulphide, or petroleum ether. It does not distill with steam. Lactic acid is decomposed when heated with dilute sulphuric acid into acetaldehyde and formic acid:



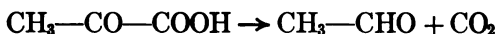
According to certain investigators this reaction is catalyzed in the production of alcohol by fermentation, the formic acid being further decomposed into hydrogen and carbon dioxide, and the hydrogen serving to reduce the aldehyde to alcohol. (See Fermentation.) The most characteristic salt of lactic acid is the zinc salt,

$\text{Zn}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 3 \text{H}_2\text{O}$ . This is soluble in 52.5 parts of water at  $15^\circ$ . Lactic acid is frequently identified by the analysis of its zinc salt.

**67. Pyruvic Acid**,  $\text{CH}_3\text{—CO—COOH}$ . This acid is formed when calcium lactate is oxidized with potassium permanganate and by other more complicated reactions:



It melts at  $14^\circ$  and boils at  $61^\circ$  under 12 mm. pressure. It is soluble in water, alcohol, and ether. Biochemical studies during recent years have made it highly probable that pyruvic acid is an intermediary product of the catabolism of carbohydrates, fats, and proteins (164, 165). An enzyme discovered by Neuberg in yeast has the property of decomposing pyruvic acid into acetaldehyde and carbon dioxide:



Pyruvic acid can be reduced to lactic acid. Its relations to other compounds will be more fully discussed later (164, 165).

**68. Stereoisomerism of the Lactic Acids.** — In discussing the peculiar relationship between the chemical structure of the amyl alcohols and the property of rotating the ray of polarized light (20) it was pointed out that optical activity in amyl alcohol is associated with the presence of

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an *asymmetric carbon atom*, *i.e.* one whose four valences are bound each to a different radical or group. Lactic acid possesses a structure which conforms with the requirements of asymmetry, and we should therefore expect to find two kinds of lactic acid, having the same chemical properties and the same physical properties (specific gravity, boiling point, melting point, etc.) except in their behavior toward polarized light. This is actually the case.

There are two classes of substances which show optical activity. Some, like quartz and sodium chlorate, produce rotation only in the crystallized state. When they are dissolved or fused the optical property disappears. Others, like active amyl alcohol, lactic acid, oil of turpentine, camphor, and sugar, are optically active whether in the crystalline or in the liquid state, or in solution. In the former case the molecules themselves do not have an asymmetric structure, but they unite to form crystals which do. We may liken this to the construction of a spiral staircase, an asymmetrical structure from symmetrical bricks. When the staircase is again resolved into its component bricks, the asymmetry disappears. The optical activity of these substances depends therefore upon a peculiar arrangement of the molecules to form an asymmetric structure. In the case of compounds which are optically active in the liquid state, the asymmetry resides in the molecules themselves.

Ordinary lactic acid, obtained either by fermentation of milk or by synthesis, is optically inactive. There is in the normal muscle tissue of all higher animals, especially after activity, an appreciable amount of dextrorotatory lactic acid. The typhus bacillus and various vibrios ferment

cane sugar with the formation of levorotatory lactic acid, and when these are mixed in equimolecular proportions there results the inactive acid identical with that obtained by synthesis or from fermented milk. Dextrolactic acid, from its presence in muscle, is called *sarcolactic acid*. It is present in muscle to the extent of .3-.5 parts per thousand. For brevity the two forms are written d- and l-lactic acids.

The reason for the difference in optical properties is best explained by the theory of Van't Hoff and Le Bel, who arrived at the same conclusions simultaneously and independently in 1874. The reasoning is briefly as follows:

The four affinities of the carbon atom are not to be conceived of as lying in the same plane, otherwise isomers should exist in compounds of the general type  $Caabb$ , where  $a$  and  $b$  represent atoms or radicals (20). No such isomerism has ever been observed. The simplest assumption that we can make with regard to the distribution in space of the four atoms or groups attached to the carbon atom is that the direction of each makes equal angles with the directions of the three others. This is equivalent to saying that the four atoms or groups are situated at the solid angles of a tetrahedron in the center of which the carbon atom itself is situated.

If the groups or atoms are all alike, they will be equally attracted by the carbon atom and the tetrahedron will be regular. If they are all different, the force with which each will be attracted will probably be different and they will arrange themselves at different distances from the carbon atom; the tetrahedron will then be irregular, *i.e.* it will have no plane of symmetry. Any compounds of the for-



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mula  $\text{CH}abc$  can exist in two forms called *enantiomorphs*, which are alike in the sense that an object is like its mirror image, but they will not be superposable.

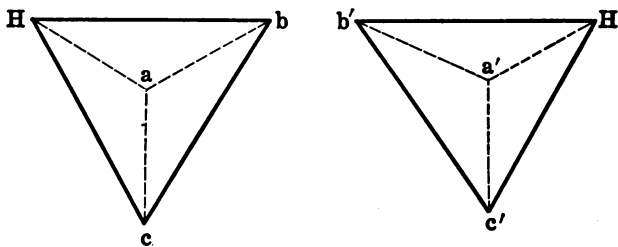


FIG. 11.

A consideration of Fig. 11 will help to make this clear: If we consider any group of three of the atoms or groups,

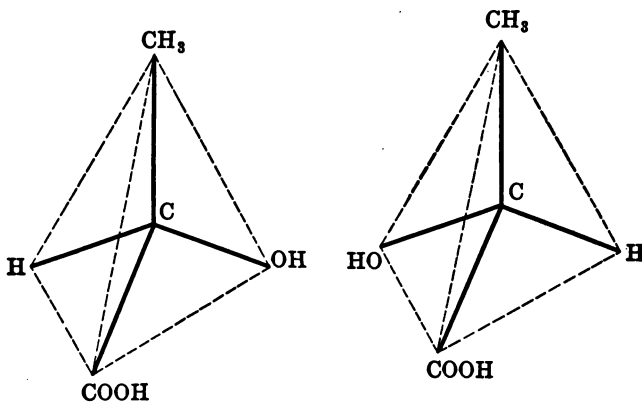


FIG. 12.

as  $\text{H}bc$ , looking toward the face about which they are arranged, any order as  $\text{H}bc$  which is clockwise in one figure will be counterclockwise in the other. If they are

at different distances from the carbon atom, any continuous curve passing through the four atoms or groups in any given sequence will form a right-handed helix in one case and a left-handed helix in the other. Such a structure would account for the observed optical properties of such compounds. According to this conception the two active lactic acids can be represented by the stereo-chemical formulæ in Fig. 12:

There is a great difference in the biological values of the d- and l-lactic acids. When the mold *Penicillium glaucum* is grown upon a solution of ammonium lactate prepared from inactive fermentation lactic acid, and containing

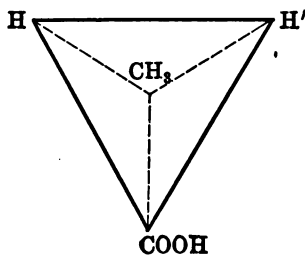


FIG. 13.

suitable inorganic salt additions, it is found after a time that the solution is dextrorotatory. The l- form is used up as a source of carbon by this mold, but not the d- form.

It has been already stated that synthetic lactic acid is inactive and consists of equal numbers of the d- and l-forms. A brief consideration will show that this must inevitably be the result. If in Fig. 13 we substitute one of the hydrogen atoms of propionic acid, H or H', by some other element or radical, we must by the law of chance substitute H as frequently as H', since in propionic acid there is a plane of symmetry from which H and H' are equidistant, and any force which comes into play in the motions of the symmetric molecules of a gas or liquid which affects one of these hydrogen atoms, has an equal

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chance of affecting the other. In the synthesis of hydroxy propionitrile the same reasoning holds good. When hydrocyanic acid condenses with acetaldehyde, Fig. 14, the addition will take place as frequently according to one scheme as the other, and the acid resulting from the hydrolysis of the nitrile must be inactive.

The formation of inactive lactic acid in fermentation involves without doubt an addition of H and OH to an inter-

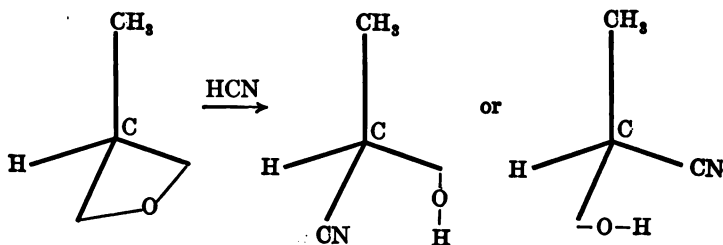
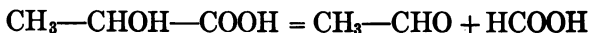


FIG. 14.

mediary product of bacterial action in which the law of chance determines the positions which each radical takes. This will be further discussed in connection with fermentation (164).

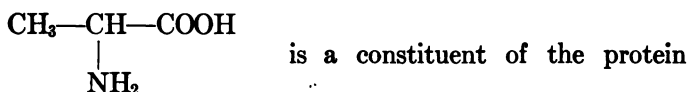
The production of l-lactic acid by certain organisms or the d-acid in the muscle tissues results from the cleavage of lactic acid from more complex compounds (sugars) which are themselves optically active and on which the positions of the H and OH groups are already determined in the molecule of the mother substance.

Lactic acid is decomposed by heating with sulphuric acid into acetaldehyde and formic acid:

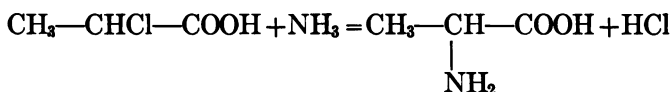


This decomposition is of interest because it shows the easiest line of cleavage of lactic acid. Acetaldehyde is without doubt formed from lactic acid in its decomposition by living tissues.

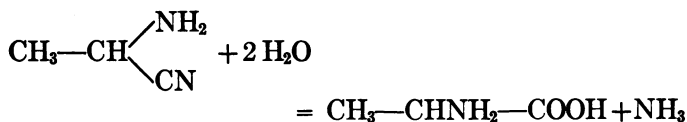
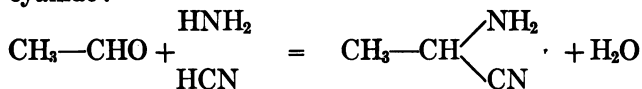
**69. d-Alanine,  $\alpha$ -aminopropionic acid,**



molecule and is formed on hydrolysis of the proteins by boiling with strong mineral acids. It is present in silk to the extent of over 20 %. It is formed, as are all the other amino acids found in proteins, by complete digestion of the latter with the enzymes, trypsin from the pancreas and erepsin from the mucous lining of the intestine. It is formed from  $\alpha$ -chlor propionic acid on treatment with ammonia :



Also by the interaction of acetaldehyde with ammonium cyanide :



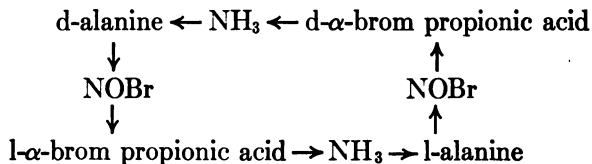
The reactions of alanine with chemical reagents are analogous to those of glycocoll (63). With nitrous acid it

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is converted into lactic acid. Since it contains an asymmetric carbon atom (68) it possesses optical activity and occurs in the d- and l- forms and in the d, l- form. Its isomerism is that of enantiomorphs and is analogous to that of the lactic acids.

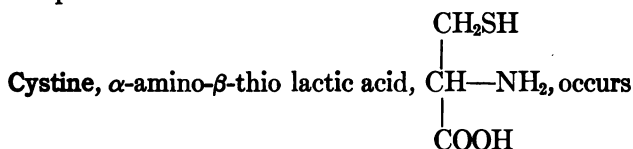
Of the two optical isomers only the d- form is of biological importance. When yeast is allowed to act on a sugar solution containing d, l-alanine, the d- form is used up as a source of energy, leaving the l- form unchanged. This method is employed generally in preparing the form of amino acids not found in nature. It is a remarkable fact that in the life processes of animals and plants, with but few exceptions, the compounds which play an important rôle are optically active, and but a single optical form occurs in nature. In no case can the optical antipode when synthesized in the laboratory be substituted for the naturally occurring form in biological processes.

A remarkable transformation of one optical form of alanine into the other occurs when d-alanine is treated with nitrosyl bromide, and the resulting l- $\alpha$ -brom propionic acid is again converted into alanine by treatment with ammonia. With each repetition of these two transformations the alanine is changed from one optical form into the other. The following scheme will make this clear :

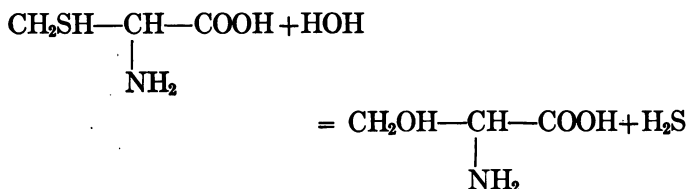


This is known from its discoverer as the "Walden transformation."

Alanine is a crystalline compound, soluble in 4.6 parts of water at 17°. It is nearly insoluble in alcohol. The ethyl ester can be distilled under diminished pressure without decomposition.



as a product of the hydrolysis of proteins. It is the only derivative of proteins which yields sulphur. Cystine is acted on by putrefactive bacteria with the liberation of hydrogen sulphide:

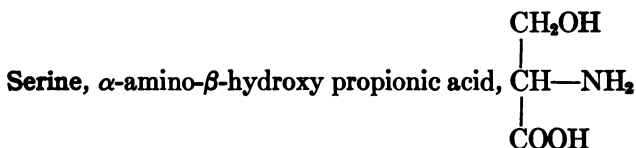


Cystine forms large hexagonal plates, and can be identified by their characteristic appearance under the microscope.

Cystine is burned to carbon dioxide, water, ammonia, and sulphuric acid in the normal body, but there occurs an anomaly of metabolism in which this amino acid is regularly excreted in the urine—the condition of cystinuria.

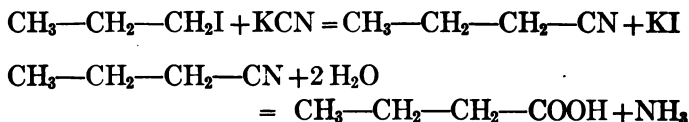
The hydrogen sulphide of the digestive tract is derived from the action of microorganisms on cystine.

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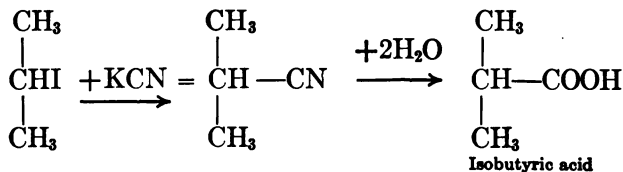


is another amino acid found among the products of the hydrolysis of the proteins. It is especially plentiful in silk. It is closely related to cystine, on the one hand, and to alanine, on the other.

**70. Butyric Acid.**—Two acids having the formula  $\text{C}_3\text{H}_7\text{COOH}$  are known. Normal butyric acid,  $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—COOH}$ , is formed from primary propyl iodide by the action of KCN and subsequent hydrolysis of the resulting nitrile:



Isobutyric acid is formed in a similar manner from secondary propyl iodide and KCN. It is therefore dimethyl acetic acid:



Normal butyric acid is found in butter, as the glycerin ester, to the extent of 2–4 %. Several kinds of micro-organisms have been described (*e.g. B. butylicus*) which

ferment sugars with the formation of butyric acid. All of these produce the normal acid. It is not produced in putrefaction. *B. hollobutyricus* can produce butyric acid from calcium lactate. The mechanism of this transformation can be discussed more satisfactorily after the properties of the unsaturated compounds have been treated (164). Normal butyric acid is a colorless, viscous liquid with a pungent, disagreeable, rancid odor. It is readily soluble in water, but is "salted out" by calcium chloride and other salts. It boils at 163°.

The calcium salt  $(C_4H_7O_2)_2Ca \cdot H_2O$  is more soluble in cold than in hot water. This peculiar behavior is probably to be explained by the formation at low temperatures of a compound between the Ca salt and water whereby a *hydrate* is produced which is soluble. This is unstable at higher temperatures, so that on heating the higher hydrate disappears and the salt with the lower water content, being insoluble, separates out.

There is no  $\alpha$ -amino butyric acid corresponding to glycocoll and alanine found in nature. In very dilute solutions (.2-1.%) and in the presence of suitable salts and a source of nitrogen, various molds, yeasts, and bacteria can employ butyric acid as a source of carbon. It is toxic, however, and possesses the property of paralyzing the motor nerve endings without interfering with the power of the muscle to contract.

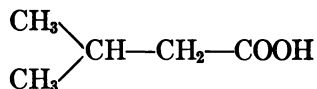
71. Isobutyric Acid,  $\begin{array}{c} CH_3 \\ \diagdown \\ CH-COOH \\ \diagup \\ CH_3 \end{array}$ , is a product of the putrefaction of proteins, where it results from the



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decomposition of valin or  $\alpha$ -amino isovalerianic acid (73). This isomer of normal butyric acid is not formed in fermentation of the sugars. Its odor is similar to that of *n*-butyric acid, but is not so offensive. It boils at  $154^{\circ}$  and, unlike its isomer, its calcium salt, is more soluble in hot water than in cold. No amino derivatives of isobutyric acid occur in nature. Its physiological and pharmacological properties closely resemble those of *n*-butyric acid.

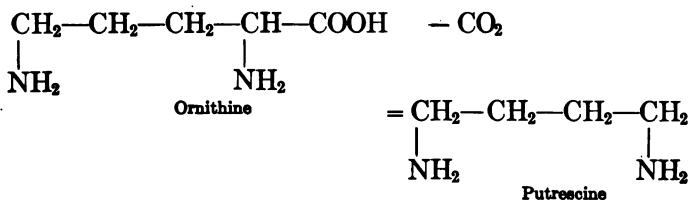
**72. Valerianic Acid,**  $\text{CH}_3-(\text{CH}_2)_3-\text{COOH}$ . — Four isomers are possible. There are but two of these which are of biological importance, the most common one being *isovalerianic* or *isovaleric*, which is isopropylacetic acid:



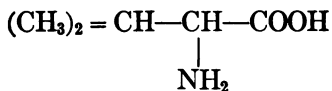
It occurs in valerian root and in other plant juices, and among the putrefaction products of proteins, where it is derived from the amino acid *leucine* (75). It results from the oxidation of fermentation amyl alcohol. B. P.  $175^{\circ}$ . It has an odor like that of old cheese.

Bromine acts on isovaleric acid, forming  $\alpha$ -brom isovaleric acid. M. P.  $44^{\circ}$ , B. P.  $150^{\circ}$  and 44 mm. pressure.

**Ornithine**,  $\alpha$ - $\delta$ -diamino valerianic acid, does not occur in nature as such but is a cleavage product of arginine (62), resulting from the hydrolysis of the guanidine radical. Ornithine is the mother substance of tetramethylene diamine, or putrescine, a base found in putrefying protein mixtures.



### 73. Amino Isovalerianic Acid, Valin,



is one of the products resulting from the hydrolysis of proteins by acids or by the digestive enzymes. It is therefore of great biological importance. It is not present in large amounts in any protein; edestin, a globulin from the hemp seed, yields more than any other protein yet examined (5.6 %).

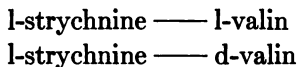
It has been prepared from sprouted lupine seeds, where it is formed by the digestion of the proteins of the seeds by proteolytic enzymes present in the germinating seeds. It has been produced synthetically by the action of ammonia on  $\alpha$ -brom valeric acid, a method analogous to that by which amino acids in general are produced (63, 69). The product of synthesis is optically inactive, while that obtained from proteins is d-valin. The synthetic amino acid can be resolved into its optical antipodes by a chemical method discovered by Pasteur. The principle of this method is as follows:

The d- and l- forms of optically active acids are exactly alike in configuration, being alike in the sense of an object

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and its mirror image, and have therefore the same physical properties (density, solubility, etc.) except as respects their influence upon polarized light (20). There are in many plants organic bases of complex constitution which contain in their molecules one or more asymmetric carbon atoms and are therefore capable of existing in optically active forms. As in the case of alanine and valin and other amino acids to be described later, there is found in nature only one optical variety, the other being incapable of playing any rôle in biological processes. Examples of such natural plant bases are quinine, strychnine, nicotine, etc.

When now an inactive mixture of d- and l- acids is treated in solution with an optically active (*i.e.* asymmetrical) base, as strychnine, there are formed salts of the acid, *e.g.* d, l-valin, and base in the following combinations:

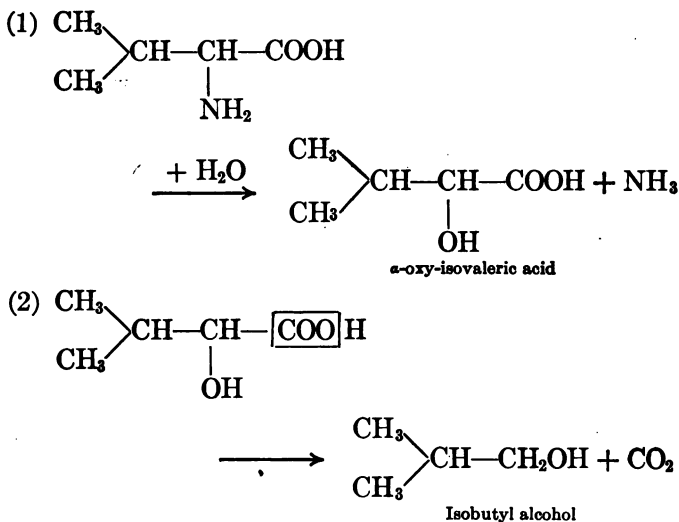


The salt molecules thus produced are no longer of the same structure and accordingly show different physical properties, as solubility, etc. The form having the greater insolubility tends therefore to crystallize out first when the solution is concentrated by evaporation of a part of the solvent. After recrystallization of the salt it is decomposed by the addition of a stronger alkali to it in solution, when the very sparingly soluble strychnine crystallizes out, leaving the optically active acid in solution as a metallic salt. The mother liquor contains the more soluble isomer.

Mention has already been made of a second method of preparing one optical isomer from the inactive mixture

which is based upon the ability of a living organism to use as food but one of the two forms (66). This method applies only to the preparation of that form which has no biological value.

Valin is the mother substance of isobutyl alcohol, as it is formed through the agency of yeast during fermentation. Yeast possesses the power to catalyze the following reactions:

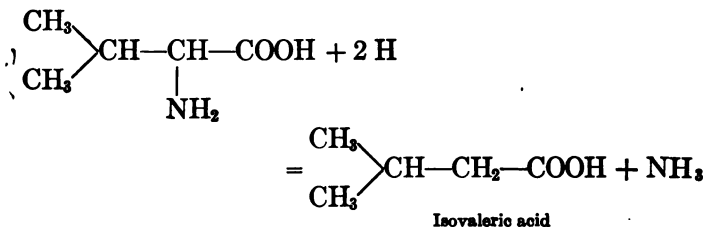


It is this type of decomposition of various amino acids which leads to the formation of fusel oil. Amyl alcohol has its origin in a similar manner from the amino acid leucine (75).

Under the influence of putrefactive bacteria (anaërobic conditions) the amino acids are deaminated, *i.e.* lose the

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amino group without losing the carboxyl group (decarboxylation).



It is by this type of reaction that the valeric acid in feces and other putrefying mixtures is formed. The anaërobic organisms have the power of obtaining oxygen from certain organic compounds, and in so doing hydrogen becomes available in the nascent state, when it effects such reactions as that just described.

**74. Caproic Acid,**  $\text{CH}_3(\text{CH}_2)_4\text{—COOH}$ . — The normal acid has been found in several plants, but it is of little biological importance. One of the isocaproic acids, isobutyl acetic,



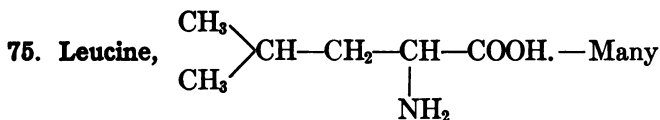
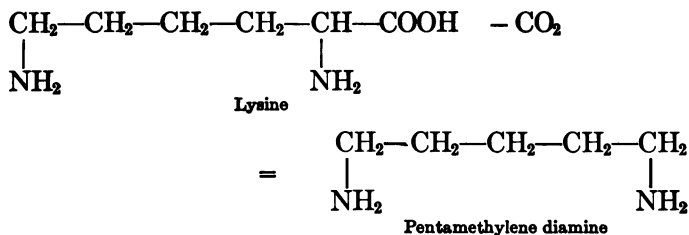
is contained in butter in the form of its glycerol ester. This isomer is of interest because one of its derivatives, viz., *α*-amino-isobutyl acetic acid, called for brevity *leucine*, is a regular constituent of the proteins, from which it results on hydrolysis.

**Lysine,** *α-ε*-diamino caproic acid, is one of the amino acids derived from the hydrolysis of proteins. It together with arginine (62) and histidine were formerly, and still to some extent are, designated as the “hexone bases” because

they each contain six carbon atoms, and it was suspected that they played a special rôle in the formation of sugar from proteins in the body. This is now known not to be the case.

Lysine is a basic amino acid, and is precipitated along with the arginine and histidine by phosphotungstic acid. The three are collectively known as the diamino acids. This is not a fortunate name, since one of the three, histidine, contains but a single amino group.

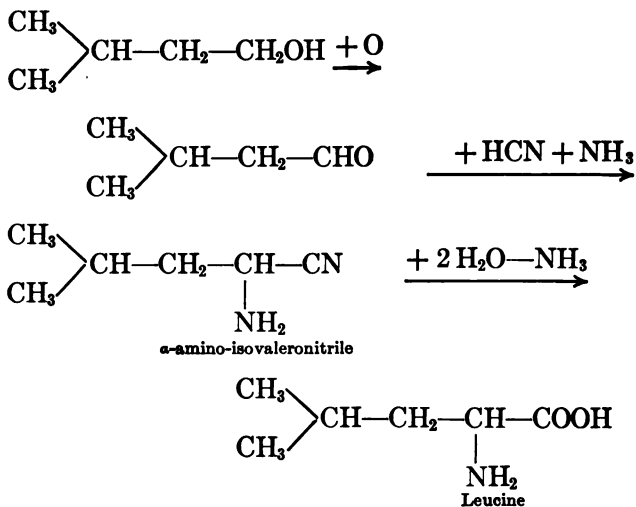
Putrefactive bacteria act on lysine, causing an elimination of carbon dioxide from the carboxyl group, forming pentamethylene diamine, *cadaverine*, which occurs in putrefying protein mixtures.



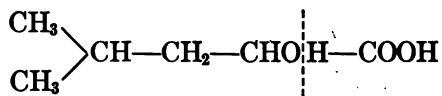
proteins yield 10–20 % of this amino acid on hydrolysis. The l- form only occurs in nature. The structure of leucine is established by its synthesis from isoamyl alcohol. This is oxidized to the corresponding aldehyde, which is then condensed with hydrocyanic acid to form the  $\alpha$ -oxynitrile of caproic acid. The latter reacts with

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ammonia with the replacement of the hydroxyl by an amino group. On hydrolysis of the nitrile to the corresponding acid inactive leucine results :

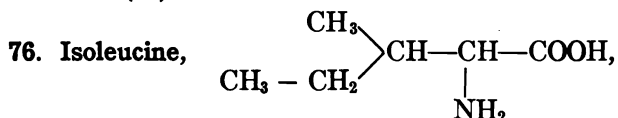


Leucine is the mother substance of the inactive isoamyl alcohol of fermentation. The reactions by which it is probably formed were described under valin (73). It is not definitely established however whether or not the steps in the reaction involve the formation of isovaleraldehyde and formic acid :



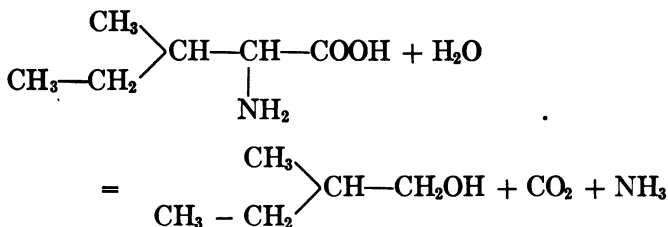
and the subsequent reduction of the aldehyde to isoamyl alcohol. Such a course is in harmony with the well-known

tendency of lactic acid to separate into acetaldehyde and formic acid (66).



$\alpha$ -amino-methyl-ethyl propionic acid, has been isolated from beet molasses and from germinated peas, and occurs among the hydrolysis products of many proteins. Since so far as is known all of the amino acids found in proteins, with the single exception of glycocoll, are indispensable in the diet, all amino acids so derived are of the greatest interest and importance.

Isoleucine is, like leucine, used by yeasts as a source of nitrogen and energy. It undergoes cleavage into an optically active amyl alcohol, secondary butyl carbinol, by the loss of carbon dioxide and ammonia:



Putrefactive organisms change isoleucine into isocaproic acid, which is found in feces (74).

**77. Higher Fatty Acids.** — From  $\text{C}_6$  upward only those members of the fatty acid series,  $\text{C}_n\text{H}_{2n}\text{O}_2$ , have any importance which contain an even number of carbon atoms. Those with an uneven number of C atoms either do not



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occur or are found but seldom and in traces. This remarkable fact has led to much speculation as to the mode of formation of the fatty acids in the plant and animal world, since any proposed series of chemical changes which lead to the building up of these acids in nature must, to constitute a tenable hypothesis, produce the even members only. Recently Miss Smedley of England has carried out synthetic work which throws much light on the mechanism of this synthesis. Its description must be deferred until certain other compounds are described (165).

The interest in the fatty acids from  $C_6$  to  $C_{18}$  depends upon their great biological value as constituents of the fats. None of the fatty acids containing more than six C atoms are found in nature in the form of their amino derivatives. By definition *fats are the esters of the triatomic alcohol glycerol with the fatty acids*. Accordingly the ester of acetic or propionic acids would be classed chemically with the fats, although they do not have the characteristic physical properties of the fats, viz. a smooth, greasy feel, insolubility in water, and oily character when melted. The term fat usually signifies only those members of the series which possess the physical properties of fats. The names of the fats are derived from the name of the fatty acid with the ending -in substituted for -ic. Thus the triester of glycerol with formic acid is *triformin*; with acetic and butyric acid, *triacetin*, *tributylin*, etc.

Since three esters are possible according as one, two, or three acid radicals are joined in ester formation with one molecule of glycerol, we distinguish mono-, di-, and tri-butylin, caproin, etc.

The fatty acids which are of biological importance as components of fats are, beginning with  $C_4$ :

		M. P.
Butyric acid	$C_4H_8O_2$	$-7.9^\circ$
Caproic acid	$C_6H_{12}O_2$	$-1.5^\circ$
Caprylic acid	$C_8H_{16}O_2$	$16.0^\circ$
Capric acid	$C_{10}H_{20}O_2$	$31.4^\circ$
Lauric acid	$C_{12}H_{24}O_2$	$43.6^\circ$
Myristic acid	$C_{14}H_{28}O_2$	$53.8^\circ$
Palmitic acid	$C_{16}H_{32}O_2$	$62.6^\circ$
Stearic acid	$C_{18}H_{36}O_2$	$69.3^\circ$
Arachic acid	$C_{20}H_{40}O_2$	$77.0^\circ$
Behenic acid	$C_{22}H_{44}O_2$	$85.0^\circ$
Lignoceric acid	$C_{24}H_{48}O_2$	$80.5^\circ$
Cerotic acid	$C_{26}H_{52}O_2$	—
Melissic acid	$C_{30}H_{60}O_2$	$88.0^\circ$

The fatty acids above  $C_6$  are very slightly soluble in water. One part of caprylic acid is dissolved in 400 parts of boiling water, but on cooling it separates almost completely in the crystalline form. The higher members are practically insoluble in water. They are more soluble in alcohol and dissolve readily in ether, chloroform, petroleum, ether, carbon tetrachloride, and in the volatile esters.

The most commonly occurring of the higher fatty acids are palmitic and stearic. They occur as esters of glycerol in both animals and plants. Their structure, as well as that of the lower members to  $C_6$  which occur in nature, is shown by synthesis and by degradation to be *normal*. By a method analogous to the formation of the ketones

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(37) the higher fatty acids are convertible into the lower members of the series.

Thus when barium stearate and barium acetate are subjected to dry distillation in a vacuum, barium carbonate and margaryl-methyl-ketone are produced:



On oxidation of the ketones the carbon chain is broken (37) and a fatty acid containing 17 carbon atoms, *margaric* acid,  $\text{C}_{17}\text{H}_{35}\text{O}_2$ , and acetic acids are formed. By repeating the ketone formation and oxidation as described the carbon chain has been shortened by  $\text{CH}_2$  in successive steps with the formation successively of palmitic, myristic, lauric, and capric acids on each occasion when the product had an even number of carbon atoms. The acids up to capric have been synthesized by building up the carbon chain, *e.g.* by the formation of the nitrile from the primary halide of nonane, and hydrolysis of the nitrile to the corresponding acid.

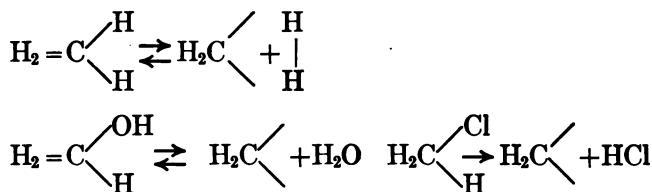
## CHAPTER VII

### THE UNSATURATED HYDROCARBONS

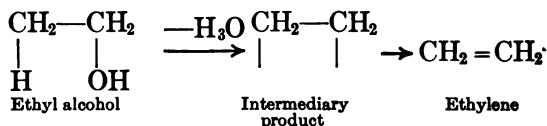
**78. Alkylenes or Olefines,  $C_nH_{2n}$ .** — When halogens react with the hydrocarbons of the paraffin series to form derivatives there is always formed one molecule of halogen acid, HCl or HBr, for each atom which enters the hydrocarbon in place of hydrogen. This is characteristic of *substitution reactions*. There is, however, another class of hydrocarbons which behave very differently toward chemical agents. When halogen comes into contact with the members of this series it is quickly absorbed or added to the molecule *without* the simultaneous formation of halogen hydride. Nascent hydrogen and the halogen acids are likewise absorbed by these hydrocarbons, the resulting compounds derived by hydrogen addition being identical with the hydrocarbons of the  $C_nH_{2n+2}$  series, and those formed by the absorption of halogen or halogen acids are identical with derivatives of the saturated hydrocarbons of the same composition, produced by substitution. Numerous efforts in the past to prepare a compound containing but one carbon atom and possessing the properties of the olefines have been unsuccessful. It has been already pointed out (2, 40) that the occurrence of many reactions of compounds containing carbon can best be explained on the assumption that very small amounts of

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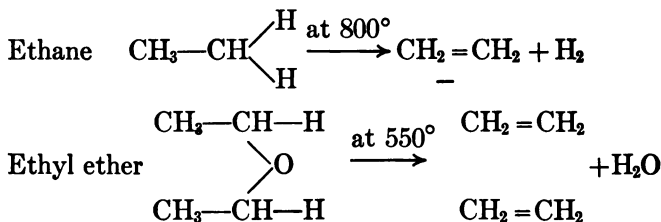
the radical methylene  $\text{CH}_2 =$  exist in dynamic equilibrium with molecules of different types. Thus the reactivity of methane, methyl alcohol, and methyl chloride depends upon the fact that each contains a relatively small per cent of *active methylene particles* at ordinary temperatures :

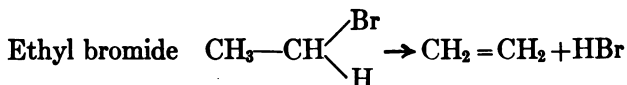
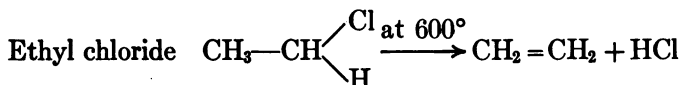
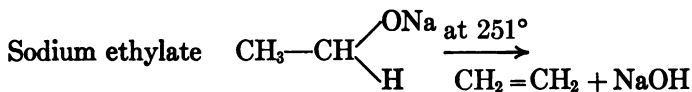


**79. Ethylene,  $\text{CH}_2 = \text{CH}_2$ .**—When ethyl alcohol is acted upon by concentrated sulphuric acid or zinc chloride, powerful dehydrating agents, water is abstracted from the molecule and the simplest of the olefines, *ethylene*, is formed. The same change is effected by heating ethyl alcohol alone to  $650^\circ$ . It separates into ethylene and water :



Further instances of the formation of ethylene by dissociation are the following :





All the above decompositions take place at the temperatures named and the products on cooling do not recombine. Ethylene can therefore be obtained quantitatively by passing, *e.g.*, ethyl chloride or bromide through a tube heated to the decomposition point.

The assumption is made that two carbon atoms in the olefines are bound together by a double bond. Adhering to the theory that in methane and its substitution products the carbon atom occupies the central position in a molecule in which the four attractive forces are directed so as to make equal angles with one another, *i.e.* as toward the four solid angles of a tetrahedron, the structures assigned to ethane and ethylene are as follows:

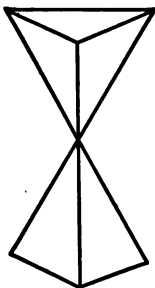


FIG. 15.

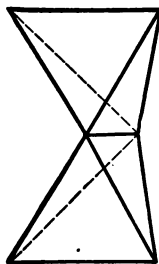
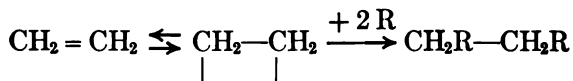


FIG. 16.

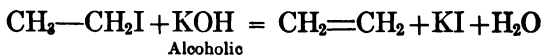
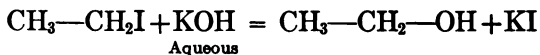
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The double bond does not bind the C atoms in a more stable union than the single bond. On the contrary, as has been stated, there is a pronounced tendency for the double bond to absorb with avidity atoms or groups and to pass into a "saturated" condition. Compounds containing the double bond, are, because of this property, spoken of as "unsaturated" compounds. The unsaturated compounds are given the ending *ene* preceded by the name of the alkyl radical from which they are derived. This high reactivity of the olefines is doubtless due to the existence of a considerable amount of dissociated particles  $\text{R}-\underset{\text{|}}{\text{CH}}-\underset{\text{|}}{\text{CH}}-\text{R}$

along with the form represented by Figure 16, for the double bond. These are in dynamic equilibrium with the undissociated form, and when compounds capable of absorption become available, the dissociated particles are rapidly removed and more double bonds dissociate until the reaction is complete:



Another method of preparing ethylene and its homologues confirms the hypothesis advanced concerning its structure. Thus ethyl iodide, when treated with aqueous KOH, yields ethyl alcohol. With alcoholic KOH solution it yields ethylene:



When ethylene is mixed with hydrogen and passed over finely divided nickel heated to 300°, addition of hydrogen atoms takes place and ethane is formed :

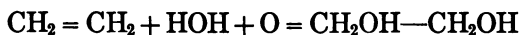


In a similar manner halogen acids are absorbed by the olefines with the formation of halogen derivatives of the paraffins :



This reaction takes place with moderate speed at about the boiling point of water, but HBr reacts much more slowly than hydriodic acid and HCl does not react at all. This finds its explanation in the fact that the acid as a molecule is not added by the olefine, but its constituent atoms; HI is an easily dissociated acid, readily liberating iodine, in the presence of even feeble oxidizing agents; while HCl is a very stable acid. HBr is intermediate in its stability. Since the bond between H and Cl must be broken before addition can take place, the firm union in HCl prevents its reaction.

The olefines are much more easily oxidized than are the saturated compounds. While ethane is not oxidized by potassium permanganate or chromic acid, the olefines are readily attacked. Dilute permanganate oxidizes ethylene to ethylene glycol :



The decolorization of dilute permanganate solution serves to detect unsaturated compounds in a mixture of hydrocarbons.

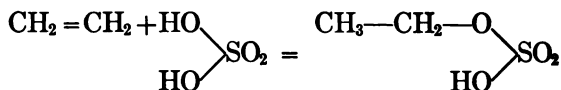


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Halogens combine with olefines to form di-halogen compounds:  $\text{CH}_2\text{X}-\text{CH}_2\text{X}$  ( $\text{X}$  = halogen). The order of reactivity is  $\text{Cl} > \text{Br} > \text{I}$ . The interaction between the halogens and olefines is greatly accelerated by light. As we have seen before in other relations, the most active halogen forms the least active halogen acid with respect to olefines. In an atmosphere of chlorine, even in diffused light, ethylene burns with the deposition of much carbon. The principal reaction is represented by the following equation:

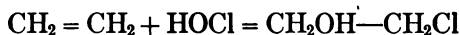


Sulphuric acid absorbs the olefines with the formation of alkyl acid sulphate:



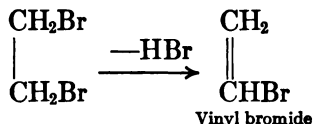
This serves as a method of separating unsaturated from saturated hydrocarbons.

Hypochlorous acid,  $\text{HOCl}$ , is absorbed by olefines. Ethylene forms ethylene chlorhydrin:

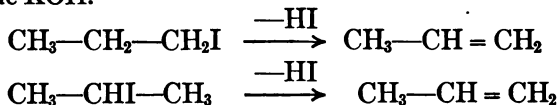


The olefines with 2, 3 and 4 atoms of carbon are gases. The higher members are liquids and solids. They are but slightly soluble in water, but dissolve in alcohol, ether, and in other organic solvents. All are combustible with a smoky flame, and mixed with air or oxygen they form dangerously explosive mixtures. Ethylene absorbs two atoms of bromine, forming *ethylene bromide*,  $\text{CH}_2\text{Br}-\text{CH}_2\text{Br}$ . Analogous compounds also result from

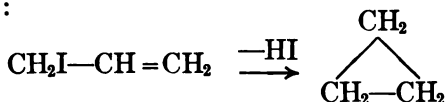
the absorption of two atoms of chlorine or of iodine. From such compounds alcoholic potassium hydroxide abstracts one molecule of halogen acid, forming bromethylene or *vinyl* bromide, chloride, etc.



80. **Propylene**,  $\text{CH}_3\text{—CH}=\text{CH}_2$ , the next homologue of ethylene, is prepared in a manner analogous to the latter, from propyl alcohol, or propyl iodide. It is instructive that both propyl iodide and isopropyl iodide yield the same propylene on the abstraction of HI by means of alcoholic KOH.



This shows that the iodine and hydrogen which are abstracted occupied positions on neighboring carbon atoms. Otherwise the normal iodide would yield a ring structure :



and should show different properties. When propylene adds on halogen acid the halogen takes its place on that carbon atom which holds the smallest number of hydrogen atoms, *i.e.* with the formation of isopropyl iodide :



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**81. Propylidene Compounds.**— It has already been pointed out (36) that the chlorides of phosphorus react with aldehydes and ketones with the replacement of

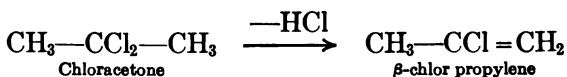
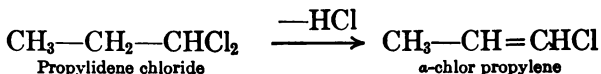
the oxygen of the carbonyl group  $\begin{array}{c} | \\ \text{CO} \\ | \end{array}$  by two chlorine atoms  $\begin{array}{c} | \\ \text{C} = \text{Cl}_2 \\ | \end{array}$ . Thus propyl aldehyde yields *propylidene chloride*:



and acetone yields *dichloracetone*:



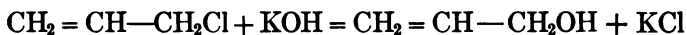
On removing one molecule of haloid acid from compounds of these types there result two isomeric chlor propylenes, having chlorine linked to a doubly linked carbon atom.



This type of halogen compound differs markedly from the alkyl halides in which the halogen is linked to a carbon atom having only single bonds. While in the alkyl halides the halogen is readily replaceable by hydroxyl, alkyl, amino groups, etc., this property is almost wholly wanting in compounds whose halogen is linked to carbon with a double bond. They do not react with alkalies to produce alcohols nor with sodium ethylate to produce ethers. Instead there are formed compounds which are substitu-

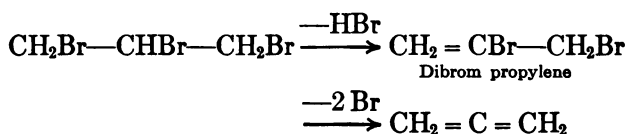
tion products of the triple bond hydrocarbons, the *acetylenes* (83). From  $\text{CH}_3\text{—CCl}_2\text{—CH}_3$  by the abstraction of two HCl there never results a diolefine  $\text{CH}_2 = \text{C} = \text{CH}_2$ , as might be expected.

An isomer of  $\alpha$ - and  $\beta$ -chlor propylene is known as allyl chloride,  $\text{CH}_2 = \text{CH—CH}_2\text{Cl}$ . This reacts just as do alkyl halides, notwithstanding the presence of the double bond in the molecule. Thus with KOH it yields allyl alcohol:



This alcohol will be described later (85).

**82. The Diolefines.**—Compounds containing two double bonds are known which have considerable importance. *Allene*,  $\text{CH}_2 = \text{C} = \text{CH}_2$ , is a gaseous hydrocarbon which can be prepared from tribrom propane by the abstraction of one molecule of HBr by means of alcoholic KOH, and the subsequent removal of the remaining two bromine atoms by zinc dust:



It is a colorless gas.

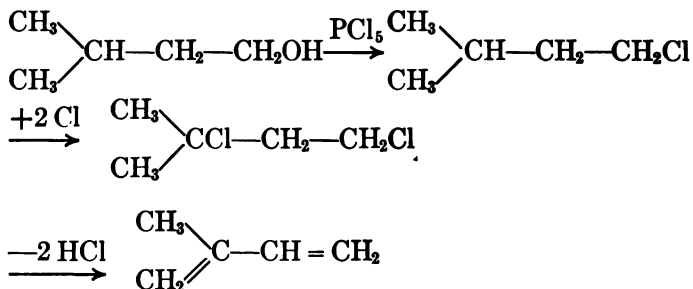
**Isoprene**,  $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CH}_2 \end{array} \text{—CH} = \text{CH}_2$ , is a liquid, B. P. 37°.

It is formed by the destructive distillation of India rubber, and also by passing turpentine through a tube

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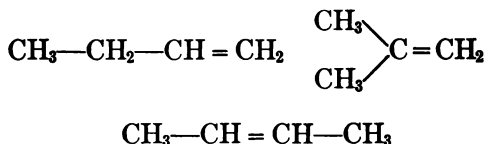
heated to redness. On treatment with acids it polymerizes, forming rubber again.

It is also formed from isobutyl carbinol, one of the amyl alcohols, by the following series of transformations :



In the presence of metallic sodium it polymerizes to a product having the physical properties of rubber, but not identical with it chemically.

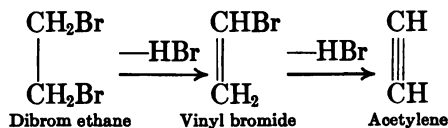
**Butylenes.** — Three butylenes are known, and this number only is theoretically possible.



They are prepared by methods analogous to propylene. They differ from ethylene in their tendency to polymerize when treated with  $\text{H}_2\text{SO}_4$  or  $\text{ZnCl}_2$ . Numerous higher homologues of this series are known.

**83. Acetylenes.** — On treatment of dibrom ethane with alcoholic KOH two molecules of HBr are abstracted with

the formation of a still more highly unsaturated compound *acetylene* :



*Acetylene* is a gas which shows all the properties of the olefines, but is more unsaturated and reacts with two molecules of halogen acid, four halogen atoms, etc. In conformity with the theory of the tetrahedral structure of the methane molecule the structure of the triple bond hydrocarbons is to be represented as in Figure 17. The carbon atoms united by a double bond possess less freedom of movement with respect to each other than those united by a single bond, and two united by a triple bond possess still less freedom of movement with respect to each other. This conception is in harmony with a special type of isomerism which is shown by compounds having the double bond as contrasted with those in which no double bond is present. That carbon atoms which are doubly and triply bound are under a strain, which leads to their tendency to change from the unstable state into other forms is further indicated by the heats of formation and of combustion of ethane, ethylene, and acetylene :

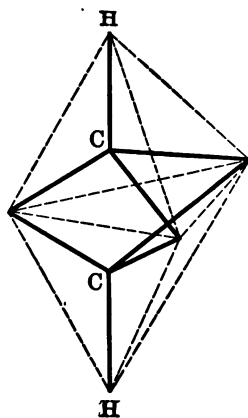


FIG. 17.

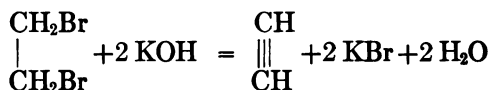
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	HEAT OF COMBUSTION	HEAT OF FORMATION
Ethane . . . . .	372.3 Cal.	23.3 Cal.
Ethylene . . . . .	341.1 Cal.	-14.6 Cal.
Acetylene . . . . .	313.8 Cal.	-51.5 Cal.

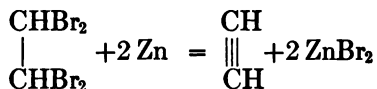
Whereas ethane is formed from its elements with the liberation of 23.3 Cal. of heat for each gram molecule, energy must be supplied to induce the formation of the double bond and still more to form the triple bond. We may liken the formation of these unsaturated compounds to the bending of a bow into a position of tension. While under a strain and possessing stored up energy it has a strong tendency to change to a body of a new conformation.

When placed under pressure greater than two atmospheres, acetylene is readily exploded by a shock. The change which takes place is one of *polymerization*, three molecules uniting to form one molecule of *benzene*. The nature of this change will be treated later (166).

*Preparation.*—Acetylene is formed from ethylene bromide by the abstraction of two molecules of HBr. This is readily effected by heating with alcoholic KOH:



Metallic zinc abstracts bromine from tetrabrom ethane in alcoholic solution, with the formation of acetylene:



A characteristic property of hydrocarbons containing the group  $\text{HC}\equiv$  is the formation of insoluble metallic compounds of the composition  $\text{C}_2\text{Ag}_2$  and  $\text{C}_2\text{Cu}_2$ , silver and cuprous acetylides respectively, when acetylene or its *monoalkyl derivatives* are passed into an ammoniacal solution of silver nitrate or of cuprous chloride. This property is utilized in analytical work to determine the acetylene content of a mixture. The quantitative capacity to absorb bromine serves as an estimation of the total unsaturated group (olefines and acetylenes), and the amount of metallic derivative forms a basis for the calculation of the content of doubly and triply unsaturated hydrocarbons in the mixture. These compounds are highly explosive when dry. They are decomposed by hydrochloric acid with the regeneration of acetylene:



Derivatives of acetylene in which both hydrogen atoms are substituted by alkyl groups do not form these metallic compounds. Acetylene is most conveniently prepared by treating calcium carbide with water. When lime and carbon (coal) are heated together in an electric furnace, the calcium oxide is reduced and calcium and carbon combine to form calcium acetylide, commonly called *calcium carbide*,  $\text{C}_2\text{Ca}$ . This compound reacts with water somewhat violently with the evolution of considerable heat and the formation of acetylene:





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When liberated through a suitable burner, acetylene burns with an intensely luminous flame. Its mixtures with air are much more dangerously explosive than are mixtures of air and coal gas, due to the reactive properties of the acetylene as compared with the paraffin hydrocarbons, and also to the wide limits of composition of air and acetylene which form explosive mixtures. Mixtures containing 3 to 82 per cent of acetylene are explosive, while the limits for coal gas are only 5 to 28 per cent. In addition the velocity of propagation of the reaction between oxygen (of the air) and acetylene is much greater in the case of the acetylene mixture, which intensifies the force of explosion.

The carbides of certain other metals yield hydrocarbons other than acetylene. Aluminum carbide yields methane on decomposition by water. Uranium carbide yields mixtures of methane and of liquid and solid hydrocarbons.

**Acetylene**,  $\text{CH}\equiv\text{CH}$ , is a gas of unpleasant odor. One volume of water dissolves about 1 volume of the gas; benzene and alcohol dissolve 4 and 6 volumes respectively, at ordinary temperatures; while acetone, which is the best solvent, dissolves 25 volumes, and much greater quantities under pressure.

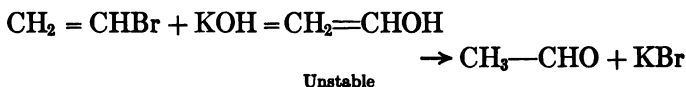
It can be synthesized from its elements by passing an electric spark between carbon poles in an atmosphere of hydrogen, a small amount of methane and ethane being simultaneously produced. It is produced in small amount when many organic substances are subjected to incomplete combustion.

Acetylene is more poisonous than ethane or ethylene. A

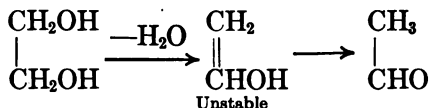
content of one volume of the gas in air produces narcosis with failure of the heart and of respiration. Higher homologues of acetylene in which the hydrogen atoms are replaced by alkyl groups are likewise known.

### SUBSTITUTION PRODUCTS OF THE UNSATURATED HYDROCARBONS

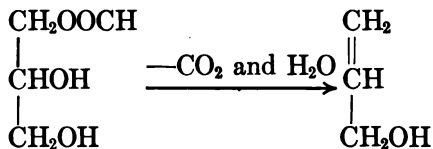
**84. Vinyl Alcohol,**  $\text{CH}_2=\text{CHOH}$ , has never been isolated and its existence is uncertain. When vinyl bromide is treated with KOH we should expect the formation of an alcohol of this type, but a rearrangement of atoms takes place with the disappearance of the double bond between the carbon atoms. When vinyl alcohol is to be expected, aldehyde is obtained:



In a similar manner the abstraction of water from glycol leads to the formation of acetaldehyde and not vinyl alcohol:



**85. Allyl Alcohol,**  $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$ , is best prepared from the monoformic ester of glycerol or *monoformin*:



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The structure of this compound is made clear by the following behavior:

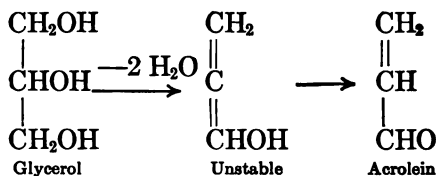
(1) It behaves like an alcohol in reacting with sodium with the evolution of hydrogen.

(2) It yields an *acetyl derivative* when treated with acetyl chloride.

(3) With nascent hydrogen ( $\text{Zn} + \text{H}_2\text{SO}_4$ ) it is converted into normal propyl alcohol. This shows that the alcohol radical is attached to an end carbon atom and is therefore a primary alcohol.

(4) The evidence that it is a primary alcohol is supported by the fact that it yields an aldehyde and an acid containing the same number of carbon atoms as the alcohol itself.

**Acrylic Aldehyde, Acrolein**,  $\text{CH}_2=\text{CH}-\text{CHO}$ , is best prepared by the abstraction of two molecules of water from glycerol. This is best effected by heating with potassium bisulphate. The reaction which takes place is probably the following:

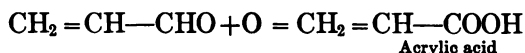


This behavior is in agreement with experience which, as pointed out above, leads to rearrangement of the atoms with the formation of an aldehyde whenever we should expect the formation of an alcohol group in union with a doubly linked carbon atom (84).

Allyl alcohol is found as an ester in the form of allyl iso-thio-cyanate,  $C_3H_5NCS$ , in the seeds of mustard. It is not free but combined with glucose as a glucoside (161).

Allyl Sulphide,  $(C_3H_5)_2S$ , is the principal constituent of oil of garlic.

Acrylic aldehyde, or *acrolein*, can in turn be oxidized to the corresponding acid, acrylic acid :

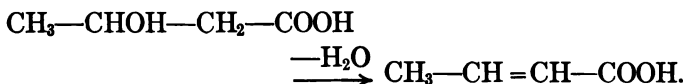


$\beta$ -Amino Acids,  $R-CH-CH_2-COOH$ , are unstable

|  
NH<sub>2</sub>

and readily split off ammonia with the formation of unsaturated compounds. Thus  $\beta$ -iodopropionic acid yields with ammonia  $\beta$ -aminopropionic acid which splits off ammonia, forming acrylic acid.

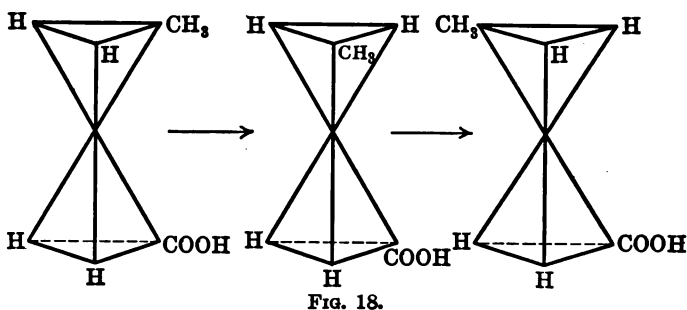
86. **Acids of the Oleic Series,  $C_nH_{2n-2}O_2$ .**—The first member of this series of acids, which differ from the saturated fatty acids by having one double bond, is acrylic acid. The second member, *methyl acrylic acid*, is known as crotonic acid. It is formed by the action of dehydrating agents upon  $\beta$ -oxy-butyric acid. The latter compound is formed directly by the condensation of two molecules of acetaldehyde by the "aldol condensation" (32, 124) :



This acid occurs in croton oil. It is a crystalline substance which melts at 72° and boils at 180°. At 19° it is soluble in 12.5 parts of water.

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There is however an *isocrotonic* acid which is an oil which boils at  $172^{\circ}$  and when maintained for a time at a temperature of  $170-180$  goes over into crotonic acid. Both of these acids yield normal butyric acid on treatment with nascent hydrogen and have, therefore, the normal carbon chain. They exhibit a kind of isomerism which cannot be explained by the ordinary constitutional formulæ. This type of isomerism, which is peculiar to the



ethylene compounds, is the necessary result of the restriction of motion of two carbon atoms linked by a double bond. Thus butyric acid may be represented as in Figure 18.

The system of the carbon atom at the center of the upper tetrahedron and its three combined atoms or groups should have no restriction as to the relative positions which they may assume with respect to the carbon atom at the center of the lower tetrahedron and its system of atoms and groups. Each should be free to rotate freely about their common axis, and all the possible arrangements probably occur; and because all are constantly shifting,

one into every other possible position, there is but one normal butyric acid.

When, as in crotonic acid, we establish the double bond (Fig. 19), the two carbon atoms affected by the double bond lose their freedom of rotating about a common axis independently of each other, and we should expect different physical properties to result from these two different structures. This type of isomerism will be more

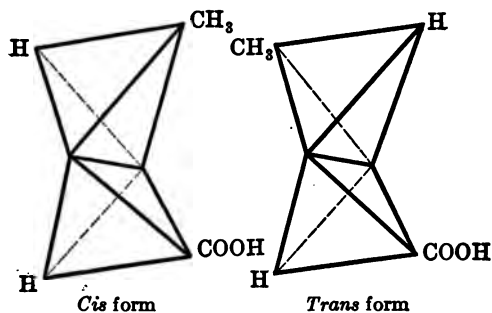


FIG. 19. — CROTONIC ACIDS.

fully dealt with in connection with maleic and fumaric acids (133). Since a considerable number of compounds of this class have been studied, in many of which it is easier to decide which compound represents the *cis* and which the *trans* form, the following generalizations may be made: The acid having the *cis* form is much the more soluble; it has also the lower melting point, and in the case of the monobasic acids is the stronger acid of the two (more highly dissociated).

In addition to the two isomers of crotonic acid just described, two other acids of the same formula are known,

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one differing from crotonic acid in the position of the double bond, the other having a branched structure:

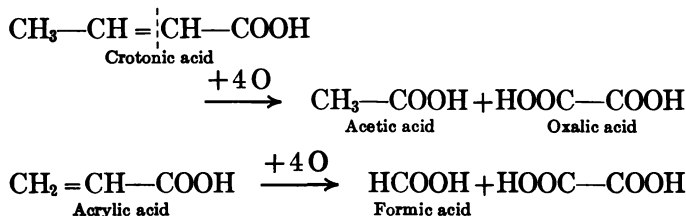


**87. Oleic Acid**,  $\text{C}_{18}\text{H}_{34}\text{O}_2$ , is widely distributed in both the animal and vegetable fats in the form of its glycerol ester, *triolein*. It differs from stearic acid in having two less hydrogen atoms and in containing a double bond. Its carbon chain has the normal structure, as is shown by its conversion into stearic acid by the absorption of two hydrogen atoms in the presence of catalyzers. Oleic acid differs widely from the saturated stearic acid. It melts at  $14^\circ$  and is therefore an oil at ordinary temperatures. In the hydrocarbons and acids of the fatty series the properties of the homologues change progressively with increasing carbon content. The longer the carbon chain, the higher the boiling point or melting point. In the unsaturated compounds the properties tend to run counterwise to this rule, *e.g.* butyric acid melts at  $-2^\circ$ , crotonic acid melts at  $72^\circ$ , stearic acid melts at  $68^\circ$ , while oleic acid melts at  $14^\circ$ . It is colorless when pure and has no odor. It undergoes transformation into its isomer, *elaidic acid*, when treated with nitrous oxide.

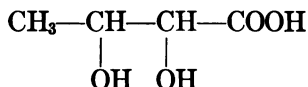
*Elaidic acid* has the same percentage composition with respect to its elements, the same molecular weight, and absorbs the same amount of iodine as does oleic acid (2 atoms), showing that it still contains the double bond. While oleic melts at  $14^\circ$ , *elaidic acid* melts at  $45-47^\circ$ . This change involves the transformation of the same type as

that represented by crotonic and isocrotonic acid. Oleic acid represents the *cis* and elaidic acid the *trans* form.

The position of the double bond in oleic acid is established by the fact that when compounds containing this linkage are oxidized, the oxidation takes place at the point of unsaturation; thus:



the oxidation in all such cases leads first to the formation of two secondary alcohol groups:



then a separation of the carbon chain. Thus oleic acid when oxidized with a dilute solution of potassium permanganate yields, first dihydroxy stearic acid, then *pelargonic* acid,  $\text{CH}_3\text{—(CH}_2)_7\text{—COOH}$ , and *azeliac* acid,  $\text{COOH—(CH}_2)_7\text{—COOH}$ . From this evidence it is concluded that the double bond in oleic acid is at the middle of the chain, *i.e.* between the ninth and tenth carbon atoms.

**88. Acids with two Double Bonds,  $\text{C}_n\text{H}_{2n-4}\text{O}_2$ ; Linolic Acid,  $\text{C}_{18}\text{H}_{32}\text{O}_2$ .**—In many plant oils there occur fatty acids which tend to take up oxygen and harden to a resin-like state. Such acids show a chemical behavior which indicates that they possess two double bonds. These are



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called linolic acid, because of their prevalence in linseed oil. Fats containing this class of acids are found especially in cottonseed, walnut, cedar, and hemp oils and to some extent in corn oil and in many other oils, but not in so high a per cent of the whole as in linseed oil. On this property depends the peculiar value of the latter oil for the manufacture of paints.

Linolic acid still remains an oil at  $-18^{\circ}$ . It absorbs 4 atoms of bromine, or two molecules of hydriodic acid. On oxidation it yields a tetrahydroxy derivative. On vigorous reduction with hydriodic acid and phosphorus, it yields stearic acid. Like oleic and stearic acids, linolic acid has the normal and not a branched structure. The tetrabromide of linolic acid is soluble in all the ordinary fat solvents except petroleum ether. This last solvent dissolves readily dibrom stearic acid, and can be employed as a useful means of distinguishing between the two.

**Acids with three Double Bonds,  $C_nH_{2n-6}O_2$ ; Linoleic Acid,  $C_{18}H_{30}O_2$ .** — This acid occurs especially in linseed oil and shows in still higher degree the "drying" property. It forms a hexabromid, and when oxidized with dilute permanganate solution a hexahydroxy stearic acid. The oils from many fishes contain fatty acids containing two and three double bonds.

It is interesting to note that the solubility of the hydroxy stearic acids in water rapidly increases with increasing number of hydroxy groups. Dihydroxy stearic acid is nearly insoluble; tetrahydroxy stearic acid, difficultly soluble; while the solubility of the hexahydroxy acid is quite marked.

## CHAPTER VIII

### THE FATS, WAXES, AND RELATED COMPOUNDS

**89. The Animal Fats.** — Most important among the animal fats are the body fats of the ox, sheep, and swine, and butter fat. As has already been stated, fats are the glycerol esters of the higher fatty acids. The body fats of animals react practically neutral, and contain but a trace of volatile fatty acids. The relative amounts of the different acids contained in the fats of different species differs widely and even the fats from the same species vary in composition with the character of the food fats. Thus *lard*, which is the collective term for the fat of the hog, may melt as low as  $28^{\circ}$  when the diet consists of corn meal only, when it contains over 90 per cent of olein; or as high as  $35.6^{\circ}$  when the animals are fed a ration of oats, peas, and barley.

From the same animal the body fats from different parts may show different melting points owing to their variable content of olein. Thus the fats surrounding the kidney may melt as high as  $43^{\circ}$  in the hog. Triolein is a liquid at  $0^{\circ}$ , while tripalmitin and tristearin melt at  $62$  and  $71.5^{\circ}$  respectively. Human fat is especially rich in olein, frequently melting as low as  $17.5^{\circ}$ , while tallow regularly melts at  $45-46^{\circ}$  and the fat of the sheep at  $46-51^{\circ}$ . The

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relative proportions of the different fats in the mixture determine the melting point.

Butter fat occupies a peculiar place among the animal fats. It consists mainly of a mixture of palmitin, stearin, and olein, but contains from 6 to 8 per cent of fatty acids volatile with steam, as glycerides, *i.e.*, butyric, caproic, caprylic, and capric, and also some lauric and myristic acids. No other fats from either animal or vegetable oils yield on saponification so high a proportion of volatile fatty acids.

**90. Vegetable Fats.** — Even greater diversity of character is found among the vegetable fats than among those from animals. *Palm oil* consists mainly of *palmitin* and olein, but contains small amounts of other glycerides. *Cocoa butter* contains about 40 % of stearin, 20 % of palmitin, 30 % of olein, and 6 % of linolein, together with some other fats.

There is a class of fats which are liquids and are therefore called oils, which are known as the *non-drying* oils to differentiate them from certain others which have different properties. The non-drying oils include olive oil, the oil of wheat, date, hazelnut, and rice. They consist mainly of triolein.

*The drying oils* are easily oxidized in the air and light, especially after being heated for a time with manganese dioxide, or lead oxide, which act as catalyzers of the oxidation process. This class includes linseed, cedar-nut, hemp, walnut, and sunflower oils, and a few others. They consist principally of triglycerides of linolic and linoleic acids.

*The semi-drying oils* consist principally of glycerides of

## The Fats, Waxes, and Related Compounds 177

oleic and linolic acids. In this group are corn and cotton-seed oil and sesame oil. These on exposure to oxygen (air) are only very slowly and incompletely converted into resinous products.

*Croton oil* deserves special mention because of its marked pharmacological action. It is pressed from the seeds of *Croton tiglium*, and is a sherry-colored viscid liquid with an acrid taste and somewhat rancid smell, and a fluorescent appearance. It is a violent purgative, in most cases a single drop being sufficient to effect intestinal activity. When rubbed upon the skin it produces rubefaction and pustular eruption.

Croton oil when saponified and subsequently acidified and distilled with steam yields about half as great a percentage of volatile fatty acids as does butter fat. Among these are formic, acetic, and valerianic acids, which are not found in butter fat.

*Castor oil* is derived from the castor bean. It consists mainly of the glyceride of *ricinoleic acid*. The latter contains eighteen carbon atoms and one double bond, but in addition it shows the reactions of a secondary alcohol, *e.g.* it forms an acetyl derivative with acetic anhydride, and yields an ester, *ricinoleic sulphonic acid*, when treated with concentrated sulphuric acid. The latter compound is used in the Turkey-red industry. The structural formula of ricinoleic acid is represented as follows :



A distinguishing property of castor oil is its insolubility in petroleum ether. It is likewise the heaviest of the fats,

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sp. gr. .960-.968. Other fats range in specific gravity from .850 to .950.

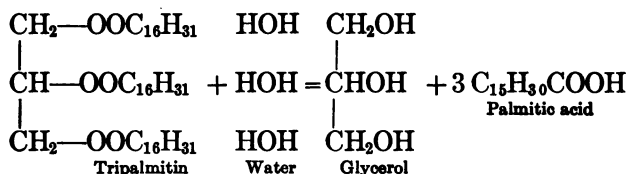
**91. Properties of the Fats.** — Since the natural fats do not represent individual chemical compounds, but mixtures of several kinds, their physical properties depend upon the proportions in which they are mixed, and especially on the content of olein. They are insoluble in water, but slightly soluble in cold alcohol. They are readily soluble in ether, petroleum ether, benzene, chloroform, and in other solvents.

The fats can be heated to 200–250° without undergoing any essential change, but above this temperature they evolve the irritating vapors of acrolein ( $\text{CH}_2 = \text{CH}-\text{CHO}$ ), which causes profuse secretion of tears. This has its origin from glycerol, from which it is formed by the loss of two molecules of water (85). This test is best carried out by heating the fat with potassium bisulphate ( $\text{KHSO}_4$ ). This acrolein test serves to distinguish the fats from the mineral oils, oily esters, and other substances having the physical properties of fats or oils.

The commercial fats on keeping become rancid. This is due to the action of the oxygen of the air, especially in the presence of light, which greatly accelerates their oxidation. In the process of becoming rancid the neutral fats become acid in reaction. Fats, especially from plant sources, are liable to become acid in reaction owing to their containing the enzyme *lipase*, which accelerates the hydrolysis of esters into alcohol and acid. In part the rancidity of impure fats is brought about by the action of bacteria on the proteins, carbohydrates, etc., with which they are contaminated.

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The fats are all saponifiable (hydrolyzable), as are other esters:



Hydrolysis can be effected by heating with water alone under pressure, but takes place slowly because of the great insolubility of fats in water. Both acids and alkalis greatly accelerate the reaction. Technically enormous quantities of fats are saponified by means of sodium hydroxide for the preparation of soap, and for the production of glycerol (glycerine). In the laboratory fats are usually saponified with an alcoholic solution of potassium hydroxide, in which the fats are much more soluble than in water. Their solution greatly facilitates the reaction.

**92. Soaps.**—Soap is made by boiling the fats with a solution of sodium hydroxide until saponification is complete. Sodium soaps are readily soluble in water, but not in strong brine, so common salt is added to precipitate the soaps. The solution from which the soap separates contains the excess of lye (NaOH) together with the glycerol formed in saponification. From the evaporated residue of this solution glycerol is prepared by distillation under diminished pressure. The soap, which has been precipitated in a flaky form, is separated, melted, and cast in molds.

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Many antiseptic substances, such as carbolic acid, salicylic acid, or cresol, thymol, tar, sulphur, naphthalene, camphor, mercury, etc., are added to soap. The finer grades are usually perfumed and frequently colored. White Castile soap is made of olive oil and sodium hydroxide. It is strongly alkaline. Green soap is made from linseed oil and potassium hydroxide, and is therefore principally potassium linolate and linoleate. *Lead soap* or *lead plaster* is prepared by saponifying olive oil with lead oxide. It is yellowish white, pliable and tenacious. It is insoluble in water, but soluble in chloroform and in benzene.

Ordinary soaps are crystalline, and the cheaper grades frequently contain rosin, sodium silicate, etc. The transparent soaps are made by dissolving crystalline soap in alcohol and then evaporating most of the solvent. They are in the colloidal state and owe their transparency to this cause.

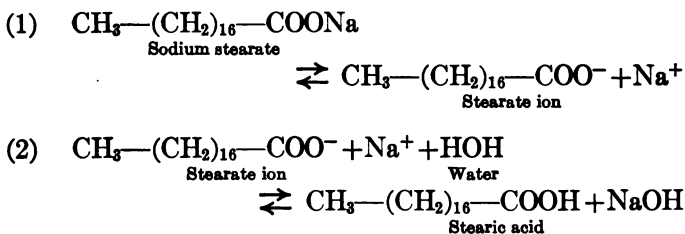
**Physiology of the Fats and Soaps.** — The body fat of animals is in part derived directly from the food, since peculiar fatty acids not found in the body fat unless contained in the food are deposited in the fat of the tissues. Carefully conducted experiments have shown that pigs and geese may accumulate much more fat in their bodies during the experimental period than was contained in the food. The animal body is therefore able to form fats from sugars and from proteins. This necessarily means that both fatty acids and glycerol are formed from other compounds. Free fatty acids are never found in the blood, and when an animal is fed free fatty acids instead of neutral fats, it

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forms glycerol to combine with them to form neutral fats before they enter the circulation.

Since the fats are not soluble in water, and there are no fat solvents in the digestive tract, fats are not capable of being absorbed directly, but must be converted into water-soluble products before absorption. The digestion of fats consists in their hydrolysis to fatty acids and glycerol. This takes place in the intestine under the influence of an enzyme, lipase, in a faintly alkaline solution. The free fatty acids at once combine with bases to form soaps. Both the soaps and glycerol are water soluble and absorbable. In the cells lining the intestine the fatty acids and glycerol are recombined to form neutral fats before entering the circulation.

**93. The Cleansing Action of Soap.** — The sodium and potassium soaps are soluble in water, and being the salts of very weak acids they undergo hydrolytic dissociation, that is, they react with water to some extent, with the formation of free fatty acid and sodium hydroxide:



This reaction is due to the fact that *salts* of *weak acids* are *strongly dissociated* while the weak acids themselves are but slightly dissociated into fatty acid ions and hydrogen



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ions. The acid ions combine with the hydrogen ions of the water to form undissociated fatty acid molecules. The acids thus liberated combine with a molecule of soap and form insoluble substances which give the milky appearance to water solutions of soap. The amount of free alkali produced depends on the degree of dilution of the soap solutions. Strong soap solution scarcely causes the pink color characteristic of alkalies with phenolphthalein, and the depth of pink steadily increases as the solution is diluted with water.

When fats come into contact with soap solutions, they tend when agitated to form an emulsion, *i.e.* the droplets of fat break up into very fine particles, each surrounded by a film of soap solution which separates each drop from its fellows and prevents their union into larger drops and consequent separation. The action of soap in removing grease is therefore twofold: the free alkali will saponify a part of the fats and thus part will pass into solution as soap; the remainder is emulsified and remains permanently suspended in the soap solution.

As the free alkali is used up by the saponification of fats, more soap dissociates to replace that which has disappeared. Soap therefore serves as a reserve supply of alkali, and in washing there is automatically maintained a constant content of hydroxyl ions in solution without at any time an undesirably high content. Soap is for this reason superior to a free alkali solution for washing. A dilute solution of the latter would show a progressive decrease in hydroxyl ions as its use progressed.

Soap does not readily remove the higher hydrocarbons,

such as vaseline, unless there is simultaneously present some fat or oil.

**94. Methods for the Characterization of the Fats.** — The chemical nature of the fats is indicated by their physical characters and by their behavior toward certain chemical reagents.

The *melting point* and the temperatures at which the fats solidify after having been melted serve to show the general nature of the fats, whether principally stearin or palmitin, or containing much olein.

The *acid number* gives the milligrams of KOH necessary to neutralize the free fatty acids contained in one gram of fat. For its determination, 1–2 grams of the fat in 12–15 c.c. of a mixture of 1 part of alcohol and 2 part of ether, which should react neutral to phenolphthalein indicator, are titrated, using this indicator with a 1/10 normal solution of potassium hydroxide in alcohol. Fresh animal fats are nearly neutral, but on becoming rancid or on long keeping the acidity rises markedly. This number gives an idea as to the state of freshness of the fats.

*Saponification Number.* — Since each molecule of fat reacts with three molecules of potassium hydroxide to form glycerol and three molecules of soap, the number of carbon atoms in the fatty acids contained in the fats will determine whether little or much alkali will be necessary to saponify a standard quantity of fat. The saponification number indicates the number of milligrams of potassium hydroxide necessary to neutralize the fatty acids derived from one gram of fat. It is determined by dissolving a weighed amount of fat in a carefully standardized solution

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of potassium hydroxide in alcohol, and heating until saponification is complete. Water is then added and the free alkali in the solution is titrated by the addition of standard acid to the neutral point, using phenolphthalein as indicator. The difference between the KOH content of the solution employed to saponify the fat and the alkali remaining unneutralized after the saponification shows how much alkali has been neutralized by the fatty acids formed. Essentially this method is a determination of the molecular weight of the fat, as the following table shows :

	MOL. WEIGHT	SAPONIFICATION No.
Butyrin . . . . .	302	557.3
Caproin . . . . .	336	436.1
Palmitin . . . . .	806	208.8
Stearin . . . . .	890	189.1
Olein . . . . .	884	190.4

*Unaponifiable Residue.* — It is obvious that the saponification number can give reliable data concerning the molecular weights of the fatty acids contained in the fats, only when glycerol is the only alcohol present in the fats. Now it not infrequently happens that there occur with the fats certain other alcohols, as cetyl and octadecyl alcohols and cholesterol ( $C_{27}H_{43}OH$ ), an alcohol of high molecular weight which is structurally very different from the higher alcohols derived from the aliphatic hydrocarbons (99). These occur free or in ester linkage with fatty acids. Cholesterol possesses physical properties very similar to

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the fats and fatty acids, and occurs free and as esters almost universally distributed in animal and plant tissues. Since these alcohols have molecular weights of 242, 270 and 384 respectively, whereas that of glycerol is but 92, the saponification number can be properly interpreted only when the content of these higher alcohols is known.

These alcohols are collectively estimated by repeatedly shaking with petroleum ether the solution of the soaps, glycerol, and higher alcohols obtained in the determination of the saponification number after again making it alkaline after the titration. Petroleum ether does not dissolve soaps, glycerol, or potassium hydroxide, but readily dissolves the higher alcohols in question. After separating the petroleum ether, filtering, and evaporating it, and again taking up the residue of higher alcohols in a fat solvent such as ether, the solution is filtered, and the solvent evaporated in a weighed dish. The residue is weighed after keeping the dish in a desiccator until its weight is constant. This weight represents the higher alcohols which were present in the sample of fat.

A few typical values of the higher alcohols in some common fats will illustrate the importance of this determination.

	UNSAAPONIFIABLE MATTER
Linseed oil	.42-1.0
Olive oil	.46-1.0
Castor oil	.30-.40
Corn oil	1.35-2.90
Wheat oil	4.45
Human fat	.33
Lard	.30-.40

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Shark liver oil	7.0-10.5
Sperm oil	37.0-41.0
Beeswax	52.0-56.0

*The Iodine Number.* — The relative content of saturated and unsaturated fatty acids in fats is determined by the capacity of the fats to absorb iodine. As an example of the determination of this value, the Hubl method will be described :

(1) A standard solution of iodine containing 25 grams of iodine and 30 grams of mercuric chloride dissolved in 500 c.c. of alcohol, free from fusel oil.

(2) A solution of sodium thiosulphate containing 24 grams of the salt per liter. This solution is standardized by determining the number of milligrams of iodine which is reduced by a cubic centimeter of the solution.

The sample of fat, .3 to .4 gram of olein-rich fats or .8 to 1 gram of solid fats, is weighed into a glass stoppered bottle and dissolved in 15-25 c.c. of chloroform. It is then heated with 25 c.c. of the iodine solution. After 6 to 10 hours 20 c.c. of a 10 % potassium iodide solution is added, the whole diluted with water, and the unabsorbed iodine is titrated by means of the sodium thiosulphate solution. The KI is added to prevent the separation of iodine in the solid state on dilution with water.

The following values illustrate the iodine values for several kinds of fats :

IODINE NUMBERS PURE FATS	
Olein	86.2
Linolein	173.6
Linolenin	262.2

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### IODINE NUMBERS OF NATURAL FATS

Linseed oil	170-200
Hempseed oil	145-150
Almond oil	93-97
Olive oil	80-88
Palm oil	51
Coconut oil	8-9
Tallow (beef)	38-45
Tallow (mutton)	35-45
Lard	50-70
Butter	26-38

### *Reichert-Meissl Number (Volatile fatty acid number).*—

It has already been stated that certain fats contain much larger amounts of the fatty acids of lower molecular weight, as butyric, caproic, etc. These acids, after saponification of the fat with an alkali and subsequent acidification with a non-volatile mineral acid, pass over with steam when the mixture of fatty acids and water is distilled. The distillate is titrated with standard alkali, using phenolphthalein as indicator. *The number of cubic centimeters of 1/10 normal alkali required to neutralize the volatile acids from 5 grams of fat constitute the Reichert-Meissl number.*

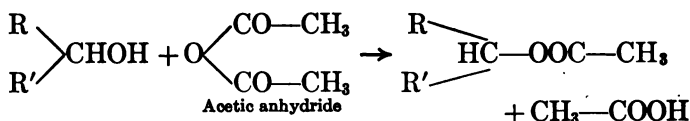
The values of the Reichert-Meissl number for some of the more important fats are as follows:

Linseed oil	0.0	Palm oil	5.0-7.0
Olive oil	0.6	Coconut oil	6.5-7.0
Lard	.7	Croton oil	12.-13.5
Tallow	.5	Butter fat	21-33.0
Goose fat	.2-.2		

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This method of examination is of great service for the examination of butter for adulteration. No other fat approximates the high value of butter fat in volatile fatty acids, and the lowering of this value by the addition of vegetable fats or the body fats of animals is readily detected.

*Acetyl Number.*—Very few of the natural fats contain hydroxylated fatty acids. Chief among these is castor oil, which in ricinoleic acid contains a secondary alcohol group (90). The amount of hydroxy fatty acids is arrived at through treatment of the fat with acetic anhydride (64) and heat, whereby the hydroxyl group of the fat forms an acetic ester :



Such esters are stable to boiling water, and the excess of acetic anhydride can be converted into acetic acid by boiling :



The acetylated fats are then separated mechanically, since they are insoluble in water and form a layer. After washing these free from acid reaction and collecting on a filter paper they are dried at 100° to constant weight. A carefully weighed sample (2-5 grams) is then saponified with an excess of carefully measured standard solution of alcoholic potassium hydroxide N/10. When saponification is complete, the same volume of N/10 acid is

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added as was added of N/10 alkali in the saponification and the solution warmed. The aqueous layer is then siphoned off through filter paper and the remaining oil is washed until all soluble acids are washed out. The filtrate and washings are titrated with N/10 alkali, using phenolphthalein as an indicator. Soluble fatty acids must be determined separately and their amount deducted from the value found.

The following table shows the values for the acetyl number of some common fats :

Linseed oil	4.0	Beeswax	15.2
Olive oil	10.5	Cod liver oil	4.8
Palm oil	18.0	Shark liver oil	12.0
Lard	2.6	Seal fat	16.5
Tallow (beef)	2.5-8.6	Spermaceti	4.5
Wool wax	23.0		

The *elaidin test* depends upon the fact that oleic acid changes from the *cis* to the *trans* form (86) with a marked rise in melting point when treated with nitrous oxide. The test is carried out by placing the oil (10 c.c.) in a test tube with nitric acid (.5 c.c.) underneath it, and placing in the acid a piece of copper (.2 gm.). If much oleic acid is present, the fat will have become solid at the temperature of 25° by the following day. Fats having two or three double bonds do not give this test.

*The Hexabromide Test.*—Dibrom and tetrabrom stearic acids result from the absorption of bromine by oleic and linolic acids or their fats. Both of these are soluble in ether. Linolenic acid having three double bonds, yields a



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hexabrom derivative, which is insoluble in ether. The test is of value therefore in detecting linolenic acid and its fats. One to two c.c. of fat are treated with 40 c.c. of ether and cooled to 5°. Bromine is then added until the brown color is permanent. Linolenic acid-containing fats yield a precipitate within three hours. It can be filtered and washed with acetic acid, alcohol, and ether, and weighed after keeping in a desiccator to constant weight.

*Separation of oleic acid as the lead soap.* The lead soap of oleic acid is soluble in ether and in benzene, while the corresponding soaps of stearic and palmitic acids are practically insoluble in these solvents. This property is made use of in effecting their separation.

**95. The Waxes.** — The surfaces of all organisms, both animals and plants, are covered with a layer of wax, which also permeates the external layers of cells. There are several kinds of waxes; all, however, are esters derived from one of the higher fatty acids and a *monatomic* alcohol of high molecular weight. They have the common property of being more or less solid at ordinary temperatures, but on warming they soften and can be kneaded. They melt at 60 to 80°. The waxes are wholly insoluble in water, but soluble in boiling alcohol, and less soluble in ether. They also dissolve in chloroform and turpentine. Like fats they produce a transparent spot when melted on paper, and confer a shiny appearance on objects coated with them. Water does not penetrate even a thin wax layer. They are not altered by light or air, or by bacteria or molds, and are proof against changes similar to rancidity. Furthermore waxes are among the poorest heat

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conductors known. Their composition is, approximately, carbon, 80 %; hydrogen, 12-13 %; and oxygen, 7-8 %.

These remarkable properties are of the very greatest biological importance. They prevent wetting of the tissues of animals and plants, and in the case of plants, eggs of insects, etc., exposed to very hot, dry atmospheric conditions, the waxy covering prevents excessive desiccation through evaporation. This layer also serves as an effective barrier against the invasion of the tissues by bacteria, and as a protection against changes of temperature.

While waxes form a layer covering the green parts of all plants, they are found in much greater abundance on some plants than others. *Carnauba wax* is found on the leaves of the Brazilian palm, *Copernicia cerifera*. It is used for candle making, polishes, wax varnishes, etc. It consists of ceryl alcohol,  $C_{26}H_{54}O$ , and myricyl alcohol, as esters of cerotic and lignoceric acids,  $C_{26}H_{52}O_2$  and  $C_{24}H_{48}O_2$ , respectively. The waxes of the gramineæ contain principally myricyl alcohol and melissic acid,  $C_{30}H_{60}O_2$ . Certain other waxes of plant origin contain palmitic acid as ester with the alcohols named, but cerotic, myristic, and melissic acids are most common. In certain cases, as *Japan wax*, obtained from several species of *Rhus*, the waxes are replaced by the hard fat palmitin. Myrtleberry wax is likewise principally palmitin. These are therefore not true waxes.

Among the animal waxes of great importance are those produced by various insects. They serve to protect the eggs and larvæ against moisture and loss of heat. *Chinese wax* produced by a coccus is ceryl cerotate; *psylla wax*,

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produced by a leaf louse in Finland, is the ester formed of psylla alcohol,  $C_{33}H_{67}OH$ , and psylla acid,  $C_{33}H_{65}O_2$ . *Bees-wax* consists principally of myricyl alcohol and cerotic and melissic acids in ester combination. It is employed by the honeybees for protecting their eggs and larvæ against cold and also for honeycomb. It also contains impurities gathered from plants.

The gland at the base of the tail in birds secretes a liquid wax which the birds spread over their feathers to render them waterproof and soft. This wax consists of palmitic, stearic, and oleic acid esters of octadecyl alcohol,  $C_{18}H_{38}O$ .

*Spermaceti* is a wax, principally cetyl palmitate, which is obtained from a cavity in the head of the sperm whale. From this cavity a canal runs to the tail and branches communicate with pockets in the panniculus. The wax is thus conveyed to all parts of the skin, which it permeates and protects from the action of the sea water. Similar esters are found in whale oil and in the oil from dolphins.

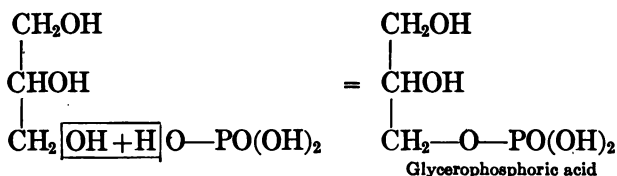
The production of spermaceti is closely analogous to the secretion of wax by the tail glands of birds and to the universal distribution of the sebaceous glands in the skin of the higher animals which produce an oily secretion of liquid wax which protects the skin and hair.

Wool wax (lanolin), the natural covering of sheep's wool, contains much cholesterol and oxysterol in the free state, and also as esters of several fatty acids, especially myristic, cerotic, and lanoceric. Wool wax also contains other higher alcohols, as carnaubyl,  $C_{24}H_{50}O$ , and lanolin alcohol,  $C_{12}H_{24}O$ .

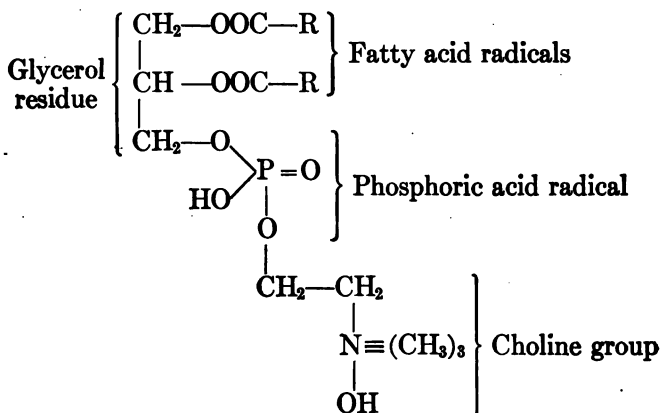
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**96. Lecithins and other Phosphatides.**—As constituents of every living cell, both animal and plant, there occur compounds closely related to the fats, called *lecithins*. These on hydrolysis yield one molecule of glycerol, two of fatty acid, one of orthophosphoric acid ( $\text{H}_3\text{PO}_4$ ), and one of choline (48).

Glycerol forms with phosphoric acid an ester, *glycerophosphoric acid*:



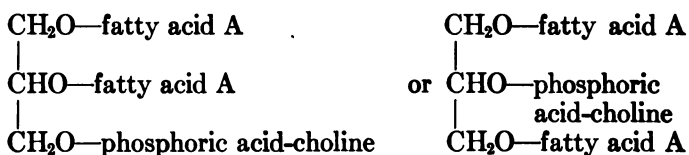
Lecithins are regarded as complexes of the following structure:



Little is known with certainty of the chemistry of the various lecithins. It is evident that different fatty acids

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in the molecule would lead to lecithins of different properties. Furthermore there is the possibility that two different fatty acids may be linked in the same molecule, forming mixed lecithins. Isomerism is likewise possible due to the different linking of the phosphoric acid-choline group :



The investigation of this class of compounds presents almost insurmountable difficulties. They are of a waxy nature, and do not form compounds with other substances which can be crystallized, for purposes of purification, and they cannot be distilled without decomposition, and have no definite melting point. There is therefore no criterion by which to judge when one is in possession of an individual chemical compound or is dealing with a mixture, except constancy of composition of the material after repeated solution and precipitation of the lecithin. This is carried out in most instances by dissolving the lecithin in ether and pouring the solution into a large volume of acetone in which lecithin is insoluble. The precipitates are always amorphous. When on repeating this method of purification the precipitate is found to contain the same percentages of nitrogen and phosphorus, these being the easiest elements to determine quantitatively, the assumption is often made that the precipitated material represents a chemical individual. Instances are known however in which two substances precipitate in fairly constant pro-

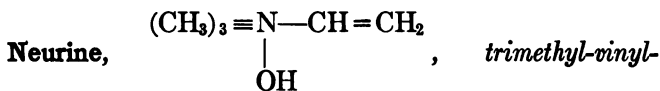
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portions under such conditions, so that such a method of purification cannot inspire much confidence.

Among the compounds formed by lecithin which have a crystalline structure, and which are serviceable for its purification, are the cadmium chloride double salt, which can be crystallized from a mixture of benzene and alcohol.

The lack of satisfactory criteria of purity for compounds of this class has rendered their investigation uninviting as compared with other lines of study. This in a measure accounts for the paucity of our knowledge of these compounds.

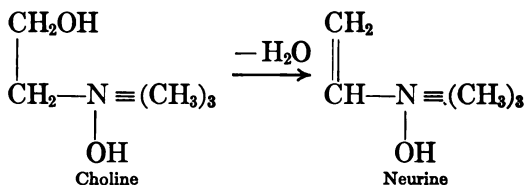
Birds when fed certain fat-free and lecithin-free foods can grow and produce eggs containing much larger amounts of lecithins than the bodies of the birds contained at the beginning of the experiment. The lecithin complex is therefore synthesized in the animal cells from its constituents. It has been pointed out (92) that fatty acids and glycerol can be formed by the animal body from sugars and proteins. The synthesis of lecithin by birds shows that the choline complex is also synthesized by the animal cells. Diets on which birds accomplished this synthesis contained neither glycol nor trimethylamine. The steps by which choline is formed are not clearly understood, but it is evident that the animal cells can, under certain conditions, form methylated nitrogen compounds, as trimethylamine, as it is known to do with tellurium and selenium (6).



*ammonium hydroxide.*—We are by no means certain that

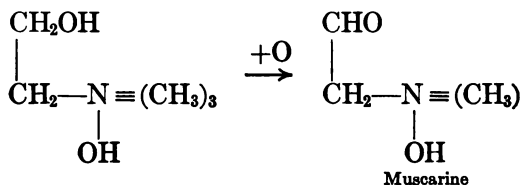
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choline is the only nitrogen base contained in the natural compounds of the lecithin type. Thudicum, a worker of distinction in this field, states that from certain phosphatides of the brain (cephalin) he obtained *neurine*. It is highly probable that bases other than choline exist in lecithins. Neurine is derived from choline by the loss of a molecule of water :



Neurine is much more toxic than choline.

Choline, being an alcohol as well as a base, can yield an aldehyde on oxidation :



• As an alcohol, choline yields esters with various acids. These in general possess pronounced pharmacological properties, being much more toxic than choline itself.

**97. Muscarine**, a highly toxic substance, occurs in some of the poisonous mushrooms, but appears not to be toxic enough to account for all of their poisonous properties.

Other phosphatides (compounds yielding fatty acids, glycerol, some nitrogen-containing base, and phosphoric acid) have been described, among them cephalin, the acids of which are more unsaturated than those of ordinary lecithins. The base is apparently not choline. It is not as yet satisfactorily studied.

**98. The Cerebrosides.** — There is found in the nervous tissue a group of substances which contain no phosphorus, but yield on hydrolysis a nitrogen-containing base of unknown chemical nature, a sugar (galactose), and a fatty acid. They are not found in embryonic nervous tissues, but develop during medullation. Two such compounds are *phrenosin* and *kerasin*. They still need further study to reveal their chemical structure.

**99. Sterols.** — The brain at different ages contains varying amounts of *cholesterol* (4–9 %) and possibly several more or less closely related compounds of this nature. Its content increases with age. As stated under waxes (95) cholesterol is an alcohol of high molecular weight. Its formula is represented by  $C_{27}H_{46}O$ . Several of its esters are known. Its structure has been in part elucidated. Its alcohol group is a secondary one, since it oxidizes to a ketone. It also contains a double bond, as shown by its forming an addition product with bromine or iodine. The structure of the rest of the molecule is not yet established. Compounds closely related to cholesterol are found in the fats of plants. These are called *phytosterols*.

Cholesterol is a crystalline solid, insoluble in water, sparingly soluble in cold, but readily in hot, alcohol, ether, acetone, chloroform, and other organic solvents. Choles-



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terol melts at  $147^{\circ}$ . It forms an acetyl derivative (ester) when heated with acetic anhydride, which melts at  $114^{\circ}$  and is useful in identifying cholesterol.

Cholesterol forms with a natural glycoside, digitonin, a compound sparingly soluble in 95 % alcohol. It is frequently precipitated in this form and weighed in its quantitative estimation.

An *ischolesterol* has been described as occurring in lanolin, and a derivative called *coprosterol* has been isolated from feces. It has no double bond and results from the reduction of cholesterol, due to bacterial action.

## CHAPTER IX

### THE DIBASIC ACIDS

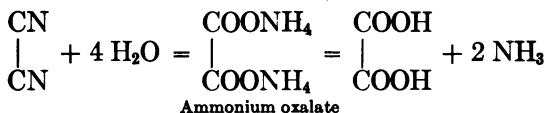
**100.** It has been shown how hydrocyanic acid reacts with water, forming ammonium formate (50). In fact, solutions of HCN are unstable, tending to react with water:



Hydrocyanic acid is therefore the nitrile of formic acid.

Cyanogen,  $\begin{array}{c} \text{CN} \\ | \\ \text{CN} \end{array}$ , on the other hand, when boiled with

acids reacts with water to form oxalic acid:



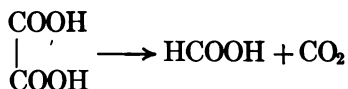
Cyanogen has therefore the double formula indicated. Oxalic acid occurs in nature in many plants—rhubarb, sorrel, etc. It is deposited as its salt, calcium oxalate, in the leaves and cells. These crystals have the appearance of envelopes. Oxalic acid is of great importance in analytical chemistry. By reason of its possession of two carboxyl groups it forms two series of salts, acid and neutral. The most important salts are the acid potassium and the neutral calcium salt. The former is present in the juices

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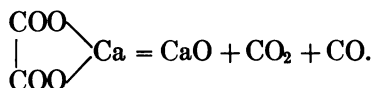
of many plants, from which it is obtained in a crystalline form on evaporation. The calcium salt is so slightly soluble in water and in dilute acetic acid that it is employed for the quantitative estimation of calcium.

The salt of urea with oxalic acid is soluble in 23 parts of water and in 60 parts of alcohol. This compound has been employed for the isolation of urea from urine.

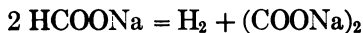
With great care and with proper conditions oxalic acid can be decomposed by heat into formic acid and carbon dioxide:



On heating strongly the formic acid decomposes into water and carbon monoxide. The calcium salt on being heated forms calcium carbonate (calcium oxide + carbon dioxide) and carbon monoxide:

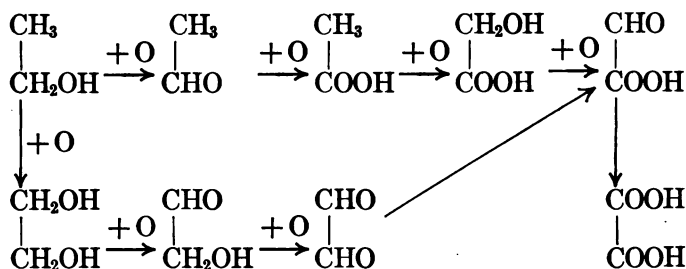


Oxalic acid can also be formed by quickly raising sodium formate to a high temperature.



Dehydrating agents such as concentrated sulphuric acid decompose oxalic acid, forming carbon monoxide, carbon dioxide, and water. This is a convenient way of preparing carbon monoxide. Characteristic of oxalic acid is its conversion into volatile products without charring when heated on platinum, and also the absence of charring when it is heated with concentrated sulphuric acid. In dilute

sulphuric acid it is easily oxidized by potassium permanganate solution. This decolorization of dilute permanganate solutions is caused by many other compounds. It is also formed by the oxidation of many organic substances such as starch, wood, etc. It results from the oxidation of alcohol by potassium permanganate. The various stages through which the oxidation may pass are illustrated by the following scheme :



This series of compounds illustrates what not infrequently happens in reactions involving the oxidation of organic compounds. The reaction does not proceed with the formation of the end products indicated by the simple equations usually written, but stepwise, and with the formation of a number of oxidation products. Only because the oxalic acid is highly resistant to further oxidation under certain conditions does the reaction stop at this point instead of going on to carbon dioxide and water. In many synthetic reactions the same type of change occurs, viz. there is a principal reaction accompanied by a number of side reactions which form by-products and diminish the yield of the desired substance. By allowing

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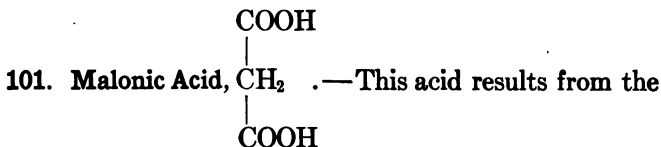
the reaction to proceed for but a short time or conducting it at low temperatures, etc., the intermediary compounds can frequently be accumulated in greater amounts.

**Properties of Oxalic Acid.** — It crystallizes from water in colorless prisms containing two molecules of water of crystallization. In this form it melts at  $101.5^{\circ}$ . On being heated for a time at  $100^{\circ}$  it loses its water and forms a white powder of *anhydrous* acid which melts at  $189^{\circ}$ . It dissolves readily in alcohol but very slightly in ether, and is insoluble in chloroform, petroleum ether, and benzene.

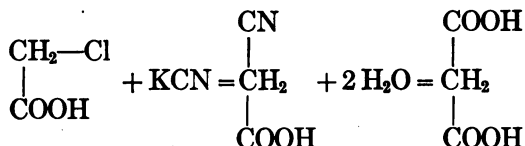
Oxalic acid is a strong acid. On evaporating a solution of sodium chloride with oxalic acid, sodium oxalate crystallizes out, and on heating a mixture of sodium chloride and oxalic acid, hydrochloric acid gas is evolved. It is a corrosive poison which acts very quickly. In general it cannot serve as a source of carbon for molds or bacteria, but there are some observations tending to show that certain organisms can so use it. Oxalic acid is produced from sugars by certain molds.

In the higher animals oxalic acid is burned to but very slight extent.

The dibasic acids form esters, amides, etc., as do the monobasic acids. There is in each case, however, a derivative possible in which but one carboxyl is substituted, as well as one derived by the reaction of both acid radicles.

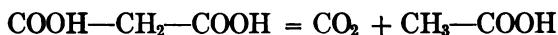


nitrile which is formed by the reaction of monochloroacetic acid with potassium cyanide:



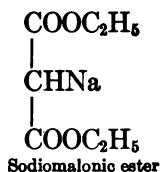
This method of synthesis makes clear its structure.

Malonic acid is a crystalline compound melting at 132°. It is found in beet juice. On heating to 140–150° it decomposes with the formation of carbon dioxide and acetic acid:



This property is common to the dibasic acids in which the two carboxyl groups are linked to one carbon atom. When heated above their melting points they lose one molecule of carbon dioxide.

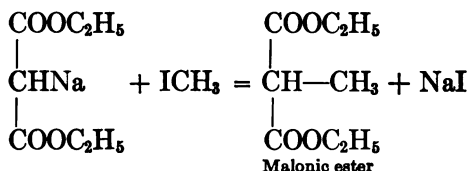
**102. Malonic Ester Synthesis.** — The most important derivative of malonic acid is its diethyl ester. It is a liquid with a slight odor which boils at 195°. It is remarkable for the peculiar behavior of the hydrogen atoms of its methylene group. When malonic ester is treated with sodium, hydrogen is evolved and a metallic derivative, *sodiummalonic ester*, is formed:



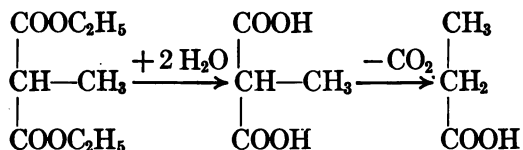
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This property of the hydrogen atoms of methylene groups being replaceable by metals is found only in compounds in which the methylene group is linked on both sides to strongly negative groups. Other instances of this character will appear later (see aceto-acetic acid, 127).

This compound reacts with alkyl iodide just as do the sodium alcoholates (24), the sodium being replaced by the alkyl groups :



The resulting alkyl derivative on saponification yields *methylmalonic acid*, which on heating above its melting point decomposes into *propionic acid*.

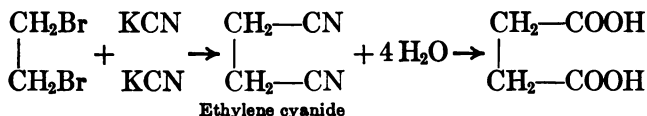


By treating methylmalonic ester with sodium the second hydrogen is replaced by metal and this in turn can be substituted by methyl, ethyl, etc. groups, which on loss of  $\text{CO}_2$  yield *dimethyl*, *methyl-ethyl*, etc., derivatives of acetic acid, viz. *isobutyric* and *isovaleric* acids. The malonic ester synthesis is therefore a general method for preparing any of the isomeric *monobasic fatty acids* as well as a great number of homologues of malonic acid.

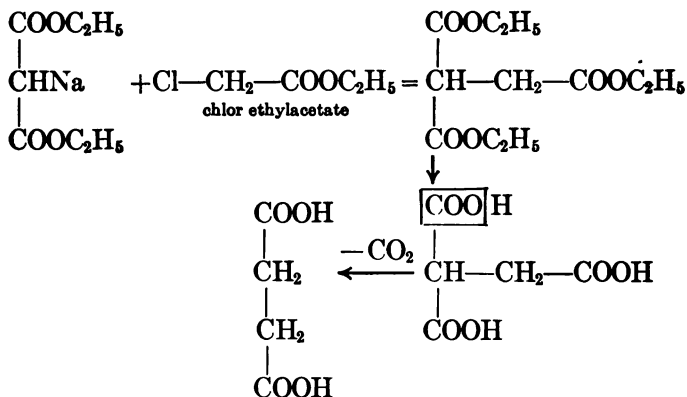
Succinic acid and urea condense to barbituric acid (139).

103. Succinic Acid. —

COOH This acid occurs in the urine after ingestion of  
 | asparagus. It is found in amber, fossilized wood,  
 CH<sub>2</sub> and many plants. It is crystalline and melts  
 | at 182°. That this acid is a homologue of  
 CH<sub>2</sub> malonic acid is shown by its synthesis from ethy-  
 COOH lene bromide, through ethylene cyanide, which  
 on hydrolysis yields succinic acid.



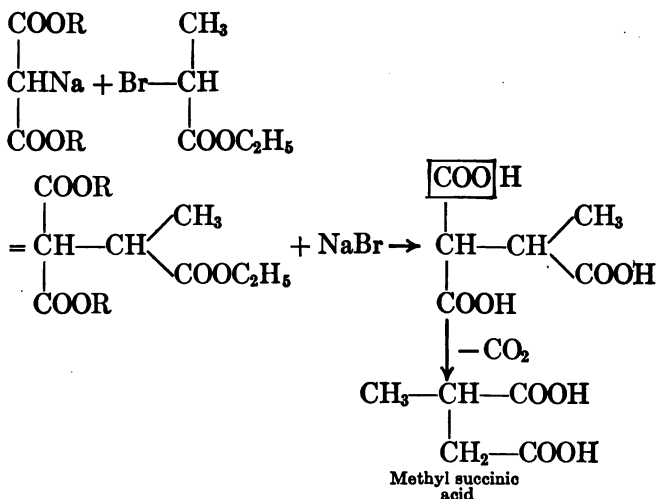
The dibasic acids can likewise be synthesized by the malonic ester synthesis. Not only does sodiomalonic ester react with alkyl halides (102), but with halogen derivatives such as the ester of chloracetic acid:





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By the same reaction substituted succinic acids can be obtained. Thus by employing  $\alpha$ -brom propionic acid methyl succinic acid is obtained.



### 104. Aspartic Acid, $\text{COOH}-\text{CH}_2-\text{CHNH}_2-\text{COOH}$ . —

The  $\alpha$ -amino derivative of succinic acid is one of the products of the hydrolysis of all proteins except the protamines (243). The carbon atom to which the amino group is attached is *asymmetric* (30) and it exists therefore in two optical forms. From the proteins the levo form is always obtained. Since it contains both carboxyl and amino groups it forms salts with both acids and bases, with the latter two series according to whether one or both of the carboxyl groups enter into salt formation. The acid salts, *i.e.* those having one free carboxyl group and the amino group, react neutral; those in which the carboxyl groups

are both neutralized by a base react alkaline through the influence of the amino group.

The normal copper salt of l-aspartic acid,  $C_4H_5O_4N \cdot Cu + 4\frac{1}{2}H_2O$ , is soluble in 2870 parts of water at ordinary temperature, and in 234 parts of boiling water.

The diethyl ester of aspartic acid boils without decomposition under 11 mm. pressure at  $126.5^\circ$ . The ethyl esters of the monobasic amino acids are hydrolyzed by a few hours' boiling with water. Aspartic ester is stable in boiling water, but is hydrolyzed by 2 hours' heating with an excess of barium hydroxide.

#### 105. Asparagine. —

$\begin{array}{l} \text{CONH}_2 \\ | \\ \text{CH}_2 \\ | \\ \text{CHNH}_2 \\ | \\ \text{COOH} \end{array}$ 
 *$\alpha$ -amino succinamide* is the half amide of aspartic acid. It is found in large amounts in the juice of sprouted seeds of the legumes. Asparagine forms large rhombic hemihedral prisms soluble in 47 parts of water at  $20^\circ$ , and insoluble in alcohol. l-asparagine has a sweet taste.

**Glutaric Acid**,  $\text{COOH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH}$ , which occurs in the washings of sheep's wool, is the next higher homologue of succinic acid. The acid itself is of biological interest because certain of its derivatives are found in nature. Chief among these are *glutamic acid*, or  $\alpha$ -amino glutaric acid, and *glutamine*, the half amide of glutamic acid. It results from the hydrolysis of propylene nitrile,  $\text{CN}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CN}$ , and can also be prepared from sodiomalonic ester by treatment with  $\beta$ -iodo propionic ester, saponifying and heating the resulting tricarboxylic acid above its melting point (102).

It crystallizes in large prisms which melt at  $97.5^\circ$  and

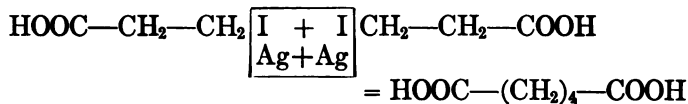
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boil at 304°. It is easily soluble in water, alcohol and ether.

**106. Glutamic Acid**,  $\text{COOH}-\text{CH}_2-\text{CH}_2-\text{CHNH}_2-\text{COOH}$ ,  *$\alpha$ -amino glutaric acid*, is present in many proteins, forming about 40 % of the total nitrogen content of the wheat proteins, gliadin and glutenin. The naturally occurring form is dextrorotatory, but its salts rotate the plane of polarized light to the left. Its diethyl ester boils under 10 mm. pressure at 139–140°. Glutamic acid is soluble at 16° in 100 parts of water. It forms salts with both acids and bases as does aspartic acid (104). Of special importance for its isolation is the hydrochloride, which is very sparingly soluble in concentrated hydrochloric acid. On saturating its solutions with hydrochloric acid gas the hydrochloric acid salt separates on cooling nearly quantitatively. This property differentiates it from aspartic acid.

**107. Glutamine**,  $\text{CONH}_2-\text{CH}_2-\text{CH}_2-\text{CHNH}_2-\text{COOH}$ , is found widely distributed in the sap of plants. After everything which is precipitable by lead has been removed from plant extracts, glutamine is precipitated by mercuric nitrate. Certain other amino acids are likewise precipitated with it, so that its purification is not simple. It is much more soluble in water than is asparagine. It seems highly probable that glutamic acid occurs within the protein molecule as glutamine. On hydrolysis with acids the amide group is converted into ammonia (90).

**108. Adipic Acid**,  $\text{COOH}-(\text{CH}_2)_4-\text{COOH}$ , is said to occur in beet juice. It is formed by the action of silver on  $\beta$ -iodio propionic acid.



It melts at 148°. It is of interest mainly because it is convertible into a ring structure. This will be described later (111).

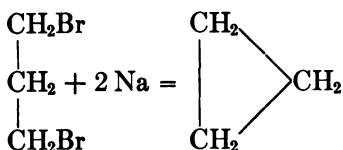
**Pimelic Acid**,  $\text{COOH}-(\text{CH}_2)_5-\text{COOH}$ , has not been found in nature. It melts at 103°, and is soluble in 25 parts of water at 20°.

**Suberic Acid**,  $\text{COOH}-(\text{CH}_2)_6-\text{COOH}$ , melts at 141°. At 15.5° one part of the acid is soluble in 600 parts of water.

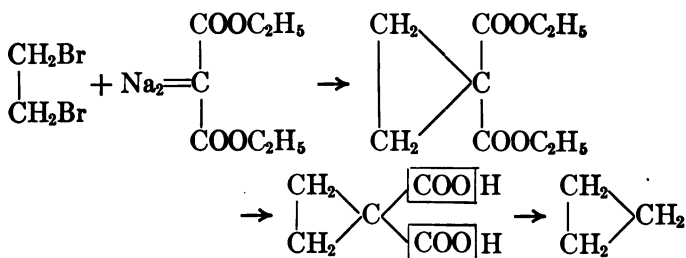
## CHAPTER X

### THE POLYMETHYLENE COMPOUNDS

109. Trimethylene,  $\begin{array}{c} \text{CH}_2 \\ | \\ \text{CH}_2 \end{array} \text{CH}_2$ , is obtained by the action of metallic sodium on trimethylene bromide:



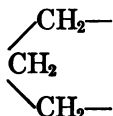
This compound is also formed by the interaction of ethylene bromide on sodiomalonic ester:



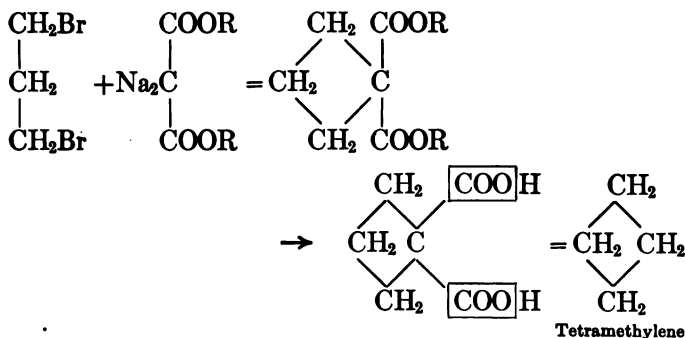
Trimethylene is isomeric with propylene,  $\text{CH}_2=\text{CH}-\text{CH}_3$ , but differs from it in its properties. Both are gases, but whereas propylene is easily oxidized by potassium permanganate, trimethylene is not attacked by this reagent. It unites with bromine only very slowly to form trimethylene bromide, and more readily with hydriodic

acid to form normal propyl iodide. The heat of combustion of trimethylene is much greater than that of its isomer (83).

The slow reaction of trimethylene with bromine indicates that the ring structure is in equilibrium with a very small amount of an active dissociation product, probably,



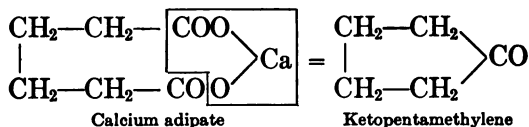
**110. Tetramethylene** is not known except in the form of certain derivatives. When trimethylene bromide reacts with sodiomalonic ester, the dicarboxylic ester of tetramethylene is formed:



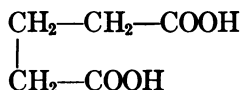
**111. Pentamethylene**,  $\begin{array}{c} \text{CH}_2-\text{CH}_2 \\ | \\ \text{CH}_2-\text{CH}_2 \end{array} \rangle \text{CH}_2$ . This hydrocarbon can be obtained by the malonic ester synthesis when tetramethylene bromide is employed with sodiomalonic ester. It is likewise formed by a series of reac-

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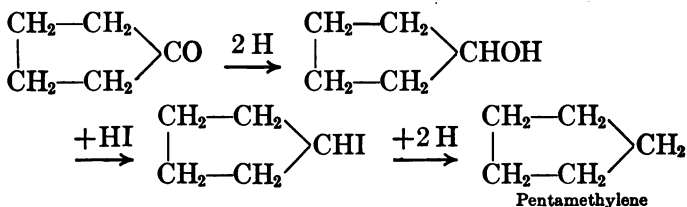
tions which are of interest, starting with the calcium salt of adipic acid :



The structure of the ketone derivative of pentamethylene is further shown by the fact that it oxidizes to glutaric acid :



Pentamethylene itself is obtained by reducing its ketone derivative to a secondary alcohol, then replacing the hydroxyl of the alcohol by iodine by treatment with hydriodic acid, followed by the replacement of the iodine by hydrogen :



Pentamethylene is a liquid boiling at 50°. It will be recalled that normal pentane boils at 37°. While the tetramethylene ring shows a tendency to open and add two halogen atoms, it does not undergo this change as readily as does trimethylene. Pentamethylene, however, is so stable that it does not react with bromine. It is exceedingly stable toward oxidizing agents, as nitric acid,

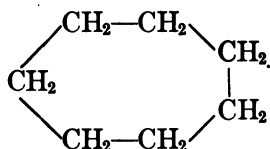
and shows none of the tendency of unsaturated compounds to condense with sulphuric acid (125).

112. Hexamethylene,  $\text{CH}_2 \begin{array}{c} \diagup \text{CH}_2-\text{CH}_2 \diagdown \\ \diagdown \text{CH}_2-\text{CH}_2 \diagup \end{array} \text{CH}_2$ , is

formed from the calcium salt of normal pimelic acid in a manner entirely analogous to that described for the formation of pentamethylene.

Hexamethylene is stable toward oxidizing agents such as potassium permanganate, and does not form an addition product with bromine. It has an odor like petroleum, and boils at  $69^\circ$ .

113. Heptamethylene,



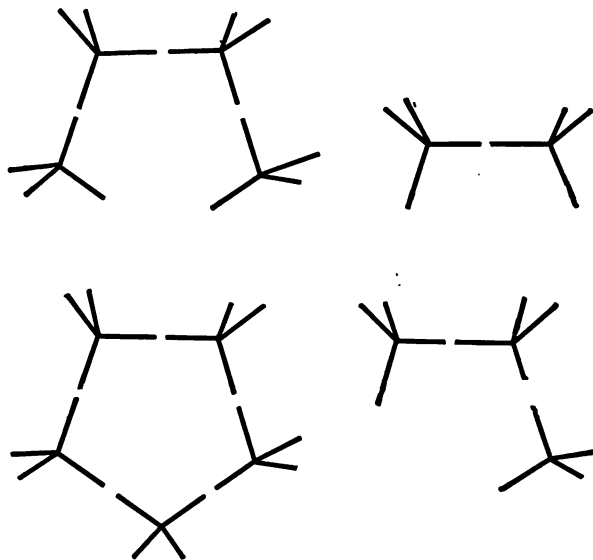
The ketone derivative of this hydrocarbon can likewise be prepared in the manner just described by dry distillation of the calcium salt of suberic acid,  $\text{COOH}-(\text{CH}_2)_6-\text{COOH}$ . And an eight-membered ring results from the calcium salt of azeliac acid,  $\text{COOH}-(\text{CH}_2)_7-\text{COOH}$ .

The stability of the polymethylene compounds increases up to pentamethylene. There is little difference in stability between this and hexamethylene, but ring structures having seven and eight carbon atoms show progressive decrease in stability. The reason for this was suggested by Baeyer, and was formulated in the following way:—



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"The four valences of a carbon atom act parallel to lines forming the corners of a tetrahedron with its center, making angles of  $109^{\circ} 28'$  with one another. The direction of the valences can be altered, but any such alteration produces a strain whose amount is proportional to the angle through which the valences are diverted."



The following figures show the angle of deviation necessary for the formation of the ring structure in the several polymethylenes :

Trimethylene	$24^{\circ} 44'$
Tetramethylene	$9^{\circ} 44'$
Pentamethylene	$0^{\circ} 44'$

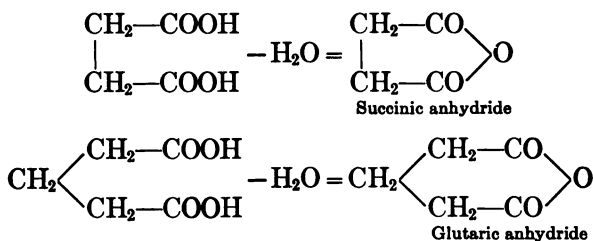
Hexamethylene	-5° 16'
Heptamethylene	-9° 33'
Octamethylene	-12° 51'

The strain is least in the case of pentamethylene among all the cyclo methylene compounds, which corresponds with its stability.

In harmony with the facts mentioned in support of the validity of the "strain theory" is the observation that heptamethylene when heated with bromine in a sealed tube changes to a methyl-substituted hexamethylene ring. These compounds are often called cyclopropane, cyclobutane, cyclopentane, etc.

The formation of a ring structure has in itself but little influence upon the properties of the hydrocarbons.

**114. Anhydrides of the Dibasic Acids.** — Oxalic and malonic acids do not form anhydrides. Succinic and glutaric acids readily lose the elements of a molecule of water from within a single molecule of the acid, forming cyclic anhydrides :



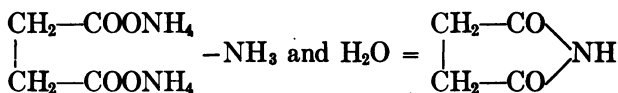
Molecular weight determinations of these anhydrides have shown that the anhydride formation does not take place between two molecules of acid. Simple solution of

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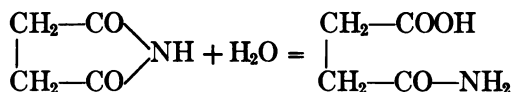
these anhydrides in water converts them back into the acids from which they were derived.

The failure of the two and three carbon dibasic acids to form anhydrides is in harmony with the "strain theory" (113).

**115. Succinimide.** — When the ammonium salt of succinic acid is heated strongly to the distillation point, a molecule of ammonia and one of water are split off and a ring structure containing the *imide* group =NH is formed :



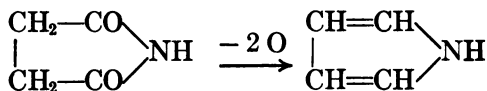
Succinimide is a crystalline compound which melts at 125° and boils at 288°. On warming with barium hydroxide solution it takes on one molecule of water, forming the half amide of succinic acid :



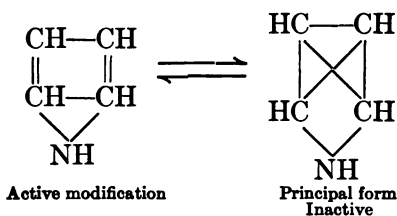
*Glutarimide* is produced in a similar manner from the ammonium salt of glutaric acid. These are examples of compounds in which nitrogen takes part with carbon in the formation of cyclic compounds.

### 116. Pyrrol,

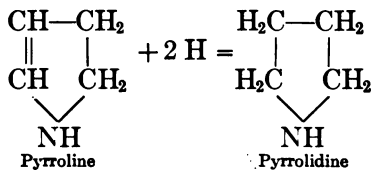
$\begin{array}{c} \text{CH=CH} \\ | \quad \diagup \text{NH} \\ \text{CH=CH} \end{array}$  is formed from succinimide by distilling the latter with zinc dust, which abstracts oxygen :



Pyrrol does not take up halogens directly, as would be expected from its possessing two double bonds. This peculiarity of certain cyclic compounds differentiates them sharply from the olefines. Pyrrol can, however, take up two atoms of hydrogen when reduced with acetic acid and zinc dust (nascent hydrogen), and the resulting *Pyrroline*, or *dihydropyrrol*, absorbs two atoms of bromine as do the olefines. This peculiar behavior has led to the assumption that instead of the double bond between the two pairs of carbon atoms one bond from each of the four is directed toward the center of the ring. This form should be very stable as compared with the double bond. The fact that nascent hydrogen is taken up by pyrrol probably finds an explanation in the existence of a small amount of the formula containing the double bond in dynamic equilibrium with the centric formula :

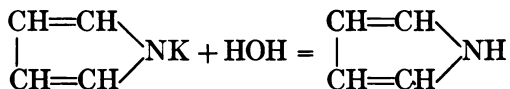


When two atoms of hydrogen are absorbed the centric formula is changed to one containing a double bond, as in pyrrolidine :



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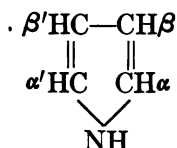
Pyrrol is a constituent of coal tar and is a product of the distillation of bones. The latter is called bone oil and contains pyridine (230) and various cyclic hydrocarbons, benzene, etc. (166), pyrrol and its homologues, together with large amounts of the nitriles of fatty acids. When agitated with dilute acid the basic compounds form salts which are soluble in water and are removed. The nitriles are saponified by boiling with alkali and the oil which remains is distilled. The fraction which distills between  $115^{\circ}$  and  $130^{\circ}$  contains the pyrrol. The hydrogen of the imino group is replaceable by metals, alkyl, acetyl, etc., and when warmed with potassium hydroxide the solid compound potassium pyrrol,  $C_4H_4NK$ , is formed. This is filtered off and decomposed by water, which regenerates pyrrol:



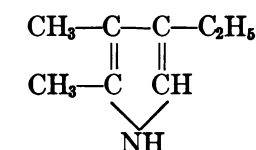
Pyrrol is a colorless liquid with an odor similar to that of chloroform. It boils at  $131^{\circ}$ , and is but slightly soluble in water. It dissolves readily in alcohol and ether. Potassium dissolves in pyrrol with the evolution of hydrogen, forming potassium pyrrol, yet pyrrol has a feebly basic character. Pyrrol gives a bright red color with a pine shaving moistened with hydrochloric acid.

**Derivatives of Pyrrol.** — While pyrrol itself is a poisonous substance and does not have a biological rôle, several of its derivatives are of great importance as constituents of the protein molecule, of chlorophyll, the green pigment of plants, of hæmin and hæmatoporphyrin, both of which

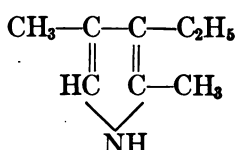
are derivatives of hæmoglobin, the respiratory pigment of the blood. Pyrrol derivatives are present in nicotine, an alkaloid contained in tobacco, and in the alkaloids of the tropine group, *e.g.* atropine, cocaine, etc., and in the bile pigments. The structure of the pyrrol derivatives is indicated thus:



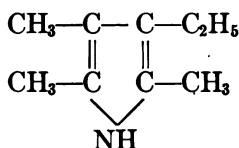
The pyrrol derivatives important from the biological standpoint are the following:



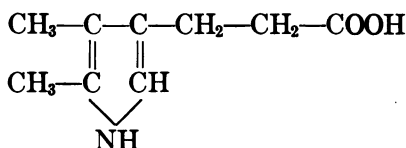
Isophæmopyrrol  
β-ethyl, α'-β'-dimethyl pyrrol



Kryptopyrrol  
α-methyl-β-ethyl-β'-methyl pyrrol



Phyllopyrrol  
α-methyl-β-ethyl-α'-β'-dimethyl pyrrol



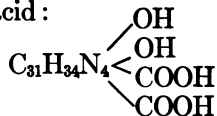
Isophonopyrrol carboxylic acid  
β-propionic acid-α', β'-dimethyl pyrrol

All four of these are derived from *hæmatin*, a substance containing iron which is present in the blood in combination with globin, a protein. The entire complex is called hæmoglobin. This has the power of combining with oxygen in loose combination and thus serves to transport oxygen throughout the body.

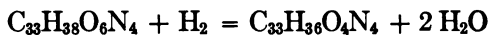
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**Hæmin**,  $C_{33}H_{32}O_4N_4FeCl$ , crystallizes out when defibrinated blood is dropped into a large volume of glacial acetic acid containing some sodium chloride, the solution being heated to  $95^\circ$ . This treatment separates the *hæmatin* from the hæmoglobin, and the compound hæmin which crystallizes out is the hydrochloride of hæmatin. It forms minute bluish black crystals with a metallic luster. It is insoluble in water, alcohol, or ether, but dissolves in chloroform containing quinine or pyridine. From such a solution it crystallizes out when alcohol containing sufficient hydrochloric or acetic acid to neutralize the base (quinine or pyridine) is added.

Hæmin contains two carboxyl groups. It combines with two molecules of hydrobromic acid. The iron becomes loosened in this reaction, and some further unknown change takes place. The dibrom compound when hydrolyzed loses its bromine, the latter being replaced by two hydroxyls. The resulting compound, known as hæmatoporphyrin, is a dihydroxy-dibasic acid :

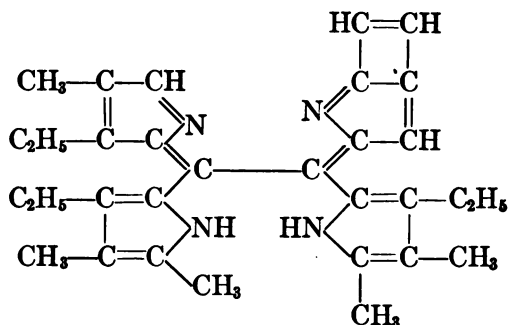


This when heated with methyl alcoholic potassium hydroxide in pyridine solution undergoes reduction and loses two molecules of water :

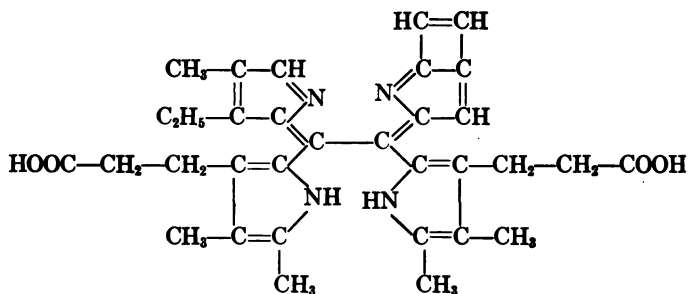


The product thus obtained is called hæmoporphyrin. It is a dibasic acid. On heating hæmoporphyrin with soda lime (a mixture of  $CaO$  and  $Na_2O$ ) the two carboxyl groups

are destroyed,  $\text{CO}_2$  being split off, and a new compound, *ætioporphyrin*, is formed. The following formulæ for the last-named derivatives have been proposed by Willstätter :



*Ætioporphyrin*,  $\text{C}_{24}\text{H}_{28}\text{N}_4$



*Hæmoporphyrin*,  $\text{C}_{24}\text{H}_{28}\text{O}_4\text{N}_4$

*Ætioporphyrin* is, according to the researches of Willstätter and his pupils, the mother substance from which both chlorophyll and hæmatin are derived. In both therefore the molecules consist of four substituted pyrrol groups. They assume that the iron in hæmatin is united with nitrogen.

In chlorophyll the condensed pyrrol nucleus possesses



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two carboxyl groups which are united with two alcohols, methyl alcohol and *phytol*, a secondary alcohol with the formula  $C_{20}H_{39}OH$ , to form an ester. Instead of iron, chlorophyll contains magnesium linked to nitrogen. A number of decomposition products of both hæmatin and chlorophyll have been described and carefully studied with a view to elucidating their chemical nature, but their description would be beyond the scope of this book. The essential fact to be borne in mind is the close chemical relationship between these plant and animal pigments.

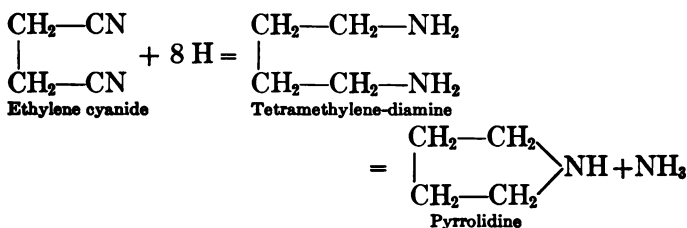
It should be pointed out as an interesting biological fact that carefully conducted feeding experiments with laboratory animals have shown that neither chlorophyll nor hæmatin is an essential constituent of the diet. The animal body is able to construct the red respiratory pigment from certain of the amino acids yielded by the proteins of the food. Probably those containing the pyrrol ring are of particular importance for this purpose.

The bile acids, bilirubin and biliverdin, are derived from disintegrated red corpuscles and are derivatives of condensed pyrrol nuclei which have their origin in the hæmatin complex of the hæmoglobin.

**117. Pyrrolidine** is of great biological interest since its derivatives, *proline* ( $\alpha$ -pyrrolidine carboxylic acid) and *oxyproline* ( $\alpha$ -oxypyrrolidine carboxylic acid), occur among the amino acids which result from the hydrolysis of proteins.

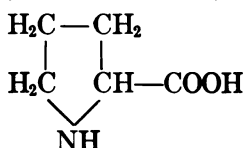
In addition to the method described for preparing

pyrrolidine (116), another which confirms its structure is its formation from ethylene cyanide. When treated with sodium and alcohol, the nascent hydrogen formed induces the following series of changes :

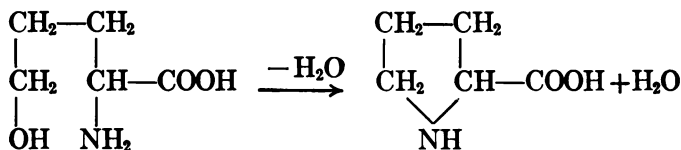


Pyrrolidine boils at 87°.

**118. Proline, *α*-pyrrolidine carboxylic acid,**



is a product of the hydrolysis of many proteins of both animal and plant origin. l-proline is the form occurring in nature. Its structure is made evident by its synthesis from *α*-amino *β*-oxyvalerianic acid. This on heating loses a molecule of water and forms proline :

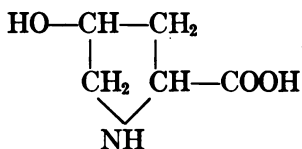


Proline is easily soluble in water. It is the only one of the naturally occurring amino acids which is readily soluble in absolute alcohol. The blue copper salt is like-

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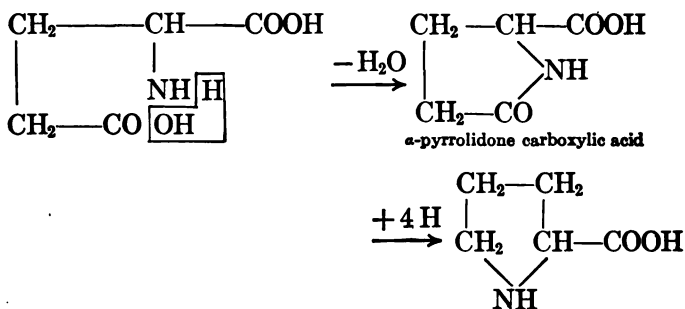
wise soluble in alcohol, and this salt is made use of in the purification. Racemic proline, the mixture of equal parts of the two optical forms, forms a copper salt which is violet when dry but absorbs moisture from the air and becomes blue again. Proline forms a salt with picric acid (184) which is useful in its identification. Among the proteins gelatin yields the largest amount of this amino acid.

### 119. Oxy-Proline, *α*-oxy-pyrrolidine carboxylic acid,



occurs in gelatin. It decomposes at  $270^\circ$  with foaming. The vapors evolved give the reactions of pyrrol (116).

**120. Pyrrolidone Carboxylic Acid.**—Of theoretical interest is the property of glutamic acid (106) of separating a molecule of water when heated to  $185\text{--}190^\circ$  with the formation of a ketone derivative of proline:



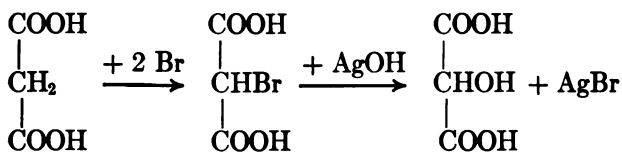
## CHAPTER XI

### HYDROXY AND KETONE ACIDS

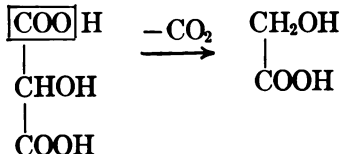
#### *Hydroxy Dibasic Acids*

**121. Tartronic Acid.**—The simplest member of the series of dibasic hydroxy acids is tartronic acid,  $\begin{array}{c} \text{COOH} \\ | \\ \text{CHOH} \\ | \\ \text{COOH} \end{array}$

This acid does not occur in nature. It is formed from malonic acid by the following reactions:

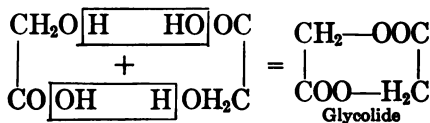


Tartronic acid melts at 187° with the loss of carbon dioxide:

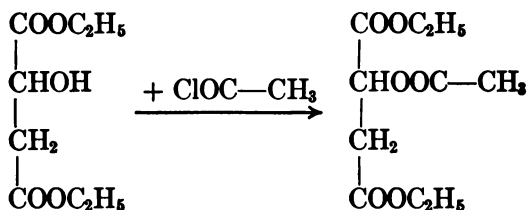


The glycolic acid formed at this temperature at once reacts with a second molecule to form an ester called *glycolide*.

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**122. Malic Acid, *hydroxysuccinic acid*,** is present in various unripe fruits, as apples, pears, etc. It is best prepared from unripe mountain ash berries or from rhubarb stalks. Its structure is indicated by its conversion into chloresuccinic acid by treatment with phosphorus pentachloride, and by the fact that the alcohol group in succinic ester reacts with acetyl chloride, forming an acetyl derivative:



On boiling the juice of rhubarb or of mountain ash berries with milk of lime, calcium malate is precipitated, since it is relatively insoluble. The salt is washed, dried, and weighed, and is then treated with the calculated amount of sulphuric acid. Insoluble calcium sulphate separates out. The solution containing the malic acid is evaporated to the point of crystallization.

Malic acid is readily soluble in water, alcohol, and ether. The calcium salt is precipitated from dilute water solutions by the addition of alcohol. Like normal cal-

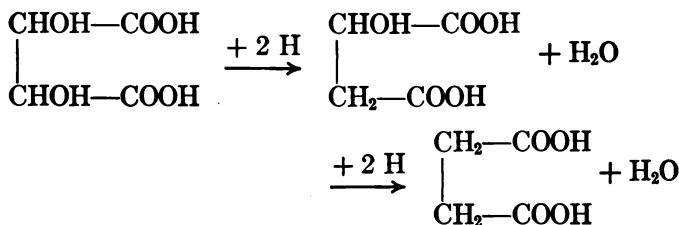
cium butyrate (70) it is more soluble in cold water than in hot and is precipitated from concentrated solutions on boiling.

Since malic acid contains an asymmetric carbon atom it exists in two isomeric forms which differ only with respect to their behavior toward polarized light. (See amyl alcohol.) The natural form is l-malic acid. When malic acid is heated to  $180^\circ$ , it loses a molecule of water and forms maleic and fumaric acids. These possess a double bond,  $\text{COOH}-\text{CH}=\text{CH}-\text{COOH}$ . They will be treated later (133).

**123. Tartaric Acids, *dihydroxy succinic acid*.**

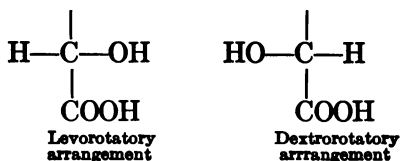


There are four acids having this composition. They all react with  $\text{PCl}_5$  to give dichlor succinic acid, and when reduced by heating with hydriodic acid they yield in turn malic and succinic acids.



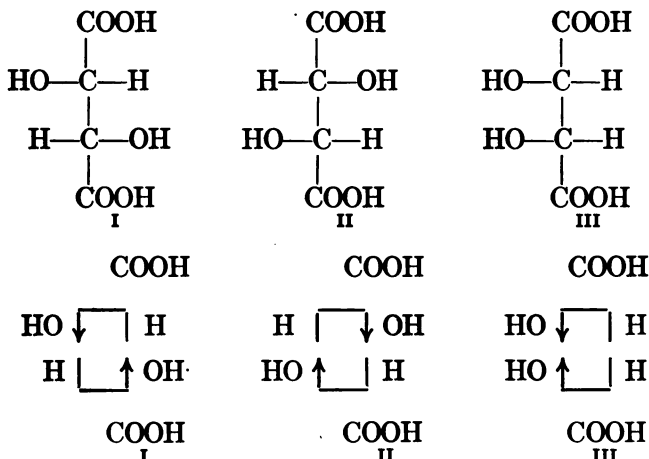
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Their differences are the result of the presence of two asymmetric carbon atoms in their molecules which makes possible enantiomorphous isomerism. (See lactic acids.) With the presence of two asymmetric carbon atoms in a molecule four modifications of the compound must exist, viz.: a right-rotating and a left-rotating form, an inactive form composed like inactive amyl alcohol or inactive lactic acid of equal molecules of the d- and l- forms, and a fourth modification, mesotartaric acid, likewise inactive, in which the configuration of one asymmetric carbon atom is the mirror image of the other one in the same molecule, *i.e.* the rotatory power is internally compensated. It is impossible to establish in the case of any two configuration formulæ, *e.g.* the lactic acids, which mode of arrangement actually represents the d- or the l- form, but if we make an arbitrary assumption in the case of one configuration, as for example that any one grouping represents levorotation, its mirror image must represent the opposite or dextrorotation:



When one of these groupings is inverted so as to be united with the other to form one molecule, the entire complex must be levorotatory as I, and its image II will be dextrorotatory. In III the two halves of the molecule will mutually neutralize the effect of each on the plane of

polarized light, and an inactive compound results. This form is called *mesotartaric acid* to differentiate it from the racemic form, which consists of both the d- and l- acids in equal amounts. Mesotartaric acid cannot be separated into d- and l-tartaric acids as can the racemic tartaric acid.



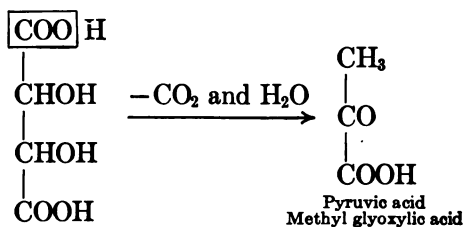
*Racemic acid* is actually a compound of one molecule of d- and one of l-tartaric acids and not simply a mixture of the two kinds of molecules. It has a different crystalline form from the two active acids, and the crystals carry water of crystallization. The racemic acid crystals are much less soluble in water than are the active acids, and have a higher melting point. The union is however a feeble one, and in solution it exists as separate molecules of the optically active acids. This is indicated by the fact that the molecular weight as shown by the



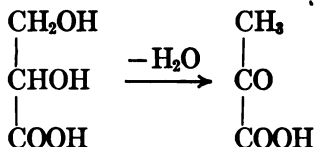
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freezing point and boiling point methods corresponds to the formula  $C_4H_6O_6$ . The esters of tartaric acids are volatile, and their vapor densities correspond to the single instead of to double molecules. Crystals of racemic acid have the composition  $2 C_4H_6O_6 + 2 H_2O$ . d- and l-tartaric acids crystallize without water of crystallization.

*Dextro-* and *levo-tartaric acids* melt at  $170^\circ$ . 100 parts of water at  $20^\circ$  C. dissolve 139.44 parts, and at  $100^\circ$  343.35 parts of either the d- or l- acids. They are much less soluble in alcohol and insoluble in ether. Tartaric acid when strongly heated with a dehydrating agent such as potassium bisulphate loses water and carbon dioxide and there distills over a ketone acid, *pyruvic acid*. This acid is likewise known as *pyroracemic acid* and as *methyl glyoxylic acid* (67).



Pyruvic acid has great biological interest. It will be further considered in connection with carbohydrate metabolism and the synthesis of fats. It is probable that the first step in the decomposition is the loss of carbon dioxide and the formation of *glyceric acid* which then loses a molecule of water. Glyceric acid itself when heated is converted into pyruvic acid.

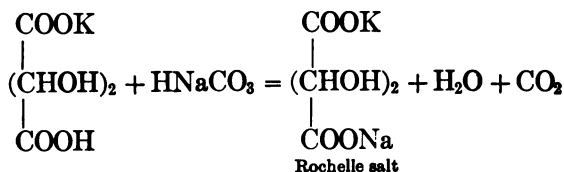


The acid potassium salt of d-tartaric acid crystallizes out of wine as alcohol accumulates during fermentation. The crude salt is known as *argol* and contains some calcium tartrate and coloring matters. The acid potassium salt is dissolved in hot water, leaving the calcium salt behind, and after treatment with animal charcoal to remove coloring matters the solution is allowed to cool



and crystallize. This salt is then known as *cream of tartar*. It is very sparingly soluble in water and still less so in alcohol. It is extensively used in baking powders.

Here it is mixed with sodium bicarbonate, with which it reacts when dissolved to form sodium potassium tartrate or *Rochelle salt*:

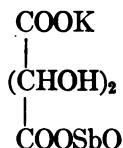


The carbon dioxide being generated throughout the dough causes it to rise into a spongy condition. Baking powders are therefore a substitute for yeast.

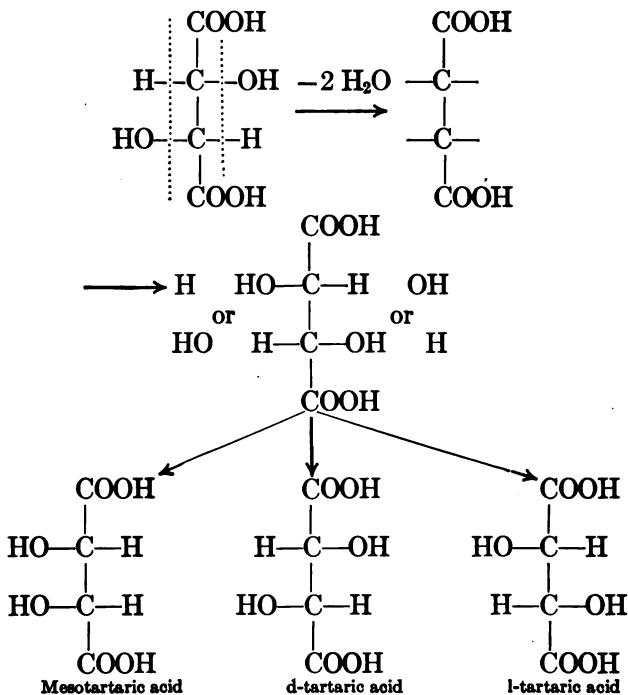
Dipotassium tartrate,  $\text{C}_4\text{H}_4\text{O}_6\text{K}_2$ , is readily soluble in water. Acid potassium tartrate dissolves antimony

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oxide,  $\text{SbO}$ , to form potassium antimonyl tartrate or tartar emetic:



Racemic acid and mesotartaric acid are both formed from d-tartaric acid by boiling with sodium hydroxide. This is explained by the assumption that water is alternately separated and added.



According to the law of chance, if water is split off from a compound and added on again in the way described, an OH group will take the place of H, just as frequently as it will replace the separated OH. Thus on repeating the separation and addition of water a sufficient number of times a state of equilibrium will be established in which all possible arrangements of H and OH groups will exist in the solution. Such a conception helps to make clear the process of racemization and likewise the transformation of certain sugars into others.

#### **SEPARATION OF RACEMIC SUBSTANCES INTO THEIR OPTICALLY ACTIVE CONSTITUENTS**

Optically active isomers show no differences in their solubility, melting point, boiling point, or amount of water of crystallization. They differ only with respect to their effect in twisting the ray of polarized light. Ordinary methods of separating mixtures depend on differences of physical or chemical properties, so that for the separation of optical isomers special procedures had to be devised. Three general methods for accomplishing such separations are known, and all of these were discovered by the brilliant French chemist, Pasteur.

The first of these depends upon the property possessed by sodium ammonium racemate, when allowed to crystallize at temperatures below 28°, of depositing side by side the sodium ammonium salt of dextro- and of levo-tartaric acids. These crystals possess hemihedral faces, and are, like mirror images, not superimposable. They

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can be recognized by their appearance and separated by picking out the two kinds of crystals by hand. On preparing the free acids from these two kinds of crystals and dissolving each kind separately they are found to have opposite optical properties. On mixing the two solutions racemic acid is re-formed.

The second method depends upon combining the d- and l- forms of acids with an optically active base. The resulting salt molecules are no longer alike in their configuration and therefore show different physical properties. Such salts can be separated by fractional crystallization. The natural bases quinine, cinchonine, brucine, and others are optically active and are useful in such separations of racemic mixtures of acids. When the racemic mixture to be separated is a base an optically active acid must be selected (73).

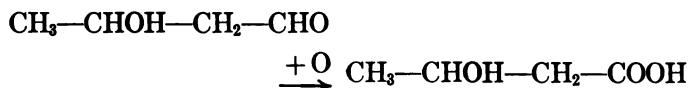
The third method devised by Pasteur for obtaining an active compound from a racemic mixture depends upon the fact that but one of the two forms of the enantiomorphous isomers has an appreciable biological value. The proteins of which the animal and plant tissues are made up are composed of optically active amino acids, and only one optical form of each occurs in nature. The sugars are likewise optically active substances. When a living organism is present in a racemic mixture of some compound which it is able to use as a source of energy, it can in general use one optical form much better than the other, and not infrequently one of such isomers is without value as a nutrient. Pasteur found that the mold *Penicillium glaucum* could make

use of the ammonium salt of d-tartaric acid but not the l- form. (See lactic acid.) Obviously this method is available only for obtaining the isomer which does not occur in nature.

**Trihydroxy Glutaric Acids**,  $\text{COOH}-\text{CH}_2\text{OH}-\text{CH}_2\text{OH}-\text{CH}_2\text{OH}-\text{COOH}$ .—There are four possible isomers having this structure. They result from the oxidation of the sugars and will be treated more in detail later (152).

**Tetrahydroxy Dibasic Acids**,  $\text{COOH}-(\text{CH}_2\text{OH})_4\text{COOH}$ , likewise are important oxidation products of the sugars. The most important are *saccharic acid*, *mucic acid*, and *isosaccharic acids*.

**124. Oxybutyric Acid and Its Related Compounds.**—The condensation of two molecules of acetaldehyde to form  $\beta$ -oxybutyric aldehyde or "aldol" has been described (32). Like other aldehydes this is oxidizable to an acid of the same number of carbon atoms,  $\beta$ -oxybutyric acid:



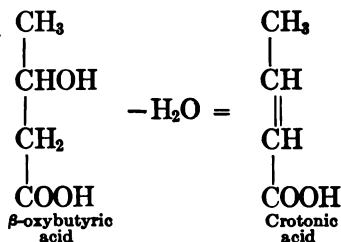
This acid has one asymmetric carbon atom and so exists in three stereoisomeric forms, dextro, levo, and inactive, of which the levorotatory form is of the greatest physiological interest since it occurs in the urine in diabetes, sometimes in surprising quantities, more than a hundred and fifty grams a day having been observed.

l- $\beta$ -oxybutyric acid closely resembles lactic acid in its behavior. It is an odorless and colorless sirup, non-

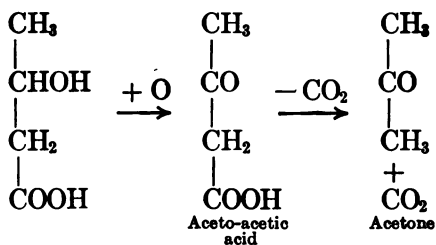
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volatile with steam, and can be obtained in the crystalline form, but the crystals are unstable. It is readily soluble in water, alcohol, ether, and acetic ether, but insoluble in benzene and petroleum ether. Its salts are all soluble in water, and difficultly soluble in alcohol, and are precipitated from alcohol by the addition of ether. The silver salt is of use in its detection. It consists of fine white needles.

On heating with water or dilute sulphuric acid  $\beta$ -oxybutyric acid is converted into crotonic acid :

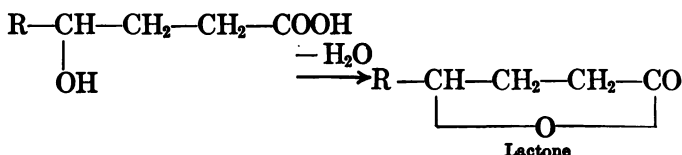


On oxidation with chromic acid it yields the ketone acid, aceto-acetic acid, which readily breaks down into acetone and carbon dioxide.

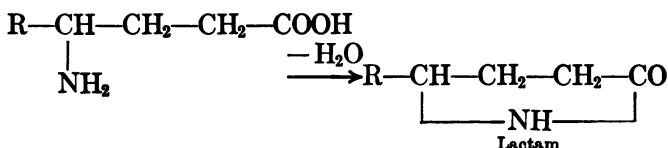


**125.  $\gamma$ -Hydroxy Acids,**  $\text{R}-\text{CHOH}-\text{CH}_2-\text{CH}_2-\text{COOH}$ , show a peculiar tendency to lose water with the formation

of internal esters called lactones. This tendency is so pronounced that many acids of this type are not known in the free state, but only as salts, esters, etc. On being set free they at once pass into the cyclic structure. Alkalies convert lactones back into the salts of the  $\gamma$ -hydroxy acids. The same conversion is in part effected by boiling with water.



126.  $\gamma$ -Amino Acids show the same tendency to lose water and form cyclic compounds. These are known as lactams:



127. Aceto-acetic Acid,  $\text{CH}_3-\text{CO}-\text{CH}_2-\text{COOH}$ , possesses great physiological interest since it occurs in the blood and urine in diabetes, where it results from the oxidation of  $\beta$ -oxybutyric acid. It is a very unstable, strongly acid sirup which absorbs moisture readily from the air. On warming it decomposes into acetone and carbon dioxide as illustrated above. In the tissues  $\beta$ -oxybutyric acid results from the oxidation of fat and in small amount from protein decomposition. This acid is particularly difficult for the diabetic to oxidize, although

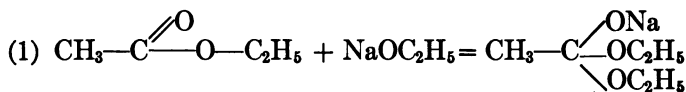


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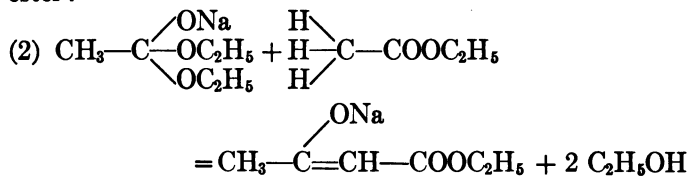
the normal organism is able to accomplish it.  $\beta$ -oxybutyric acid is partly oxidized to aceto-acetic acid in the blood and the decomposition of the latter acid into acetone and carbon dioxide takes place spontaneously, so that in the severe diabetic blood there are always found the three compounds,  $\beta$ -oxybutyric and aceto-acetic acids and acetone, together.

A certain peculiarity in the isomerism displayed by aceto-acetic acid, together with the great importance of its ester in synthesis, make it desirable to describe the behavior of the latter in some detail.

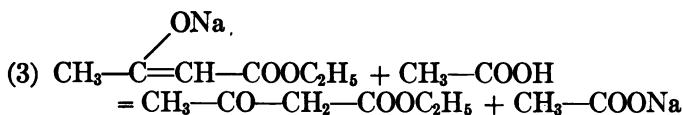
**Aceto-acetic Ester** is formed by the reaction of ethyl acetate with sodium ethylate. There are three stages to the reaction: the formation of an addition product between ethyl acetate and sodium ethylate:



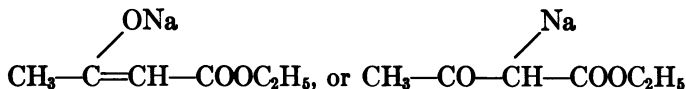
This then reacts with a second molecule of ethyl acetate to form the sodium compound of aceto-acetic ester:



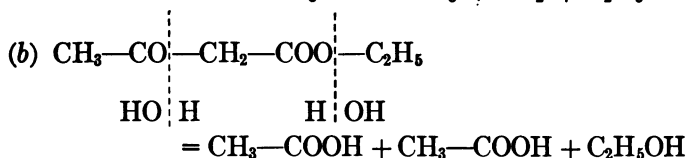
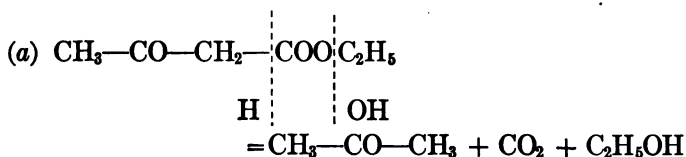
The ethyl aceto-acetate is formed on treating the sodium compound with an acid. This is known as Claisen's synthesis:



The sodium derivative, as will appear later, may have either of the two following structures:



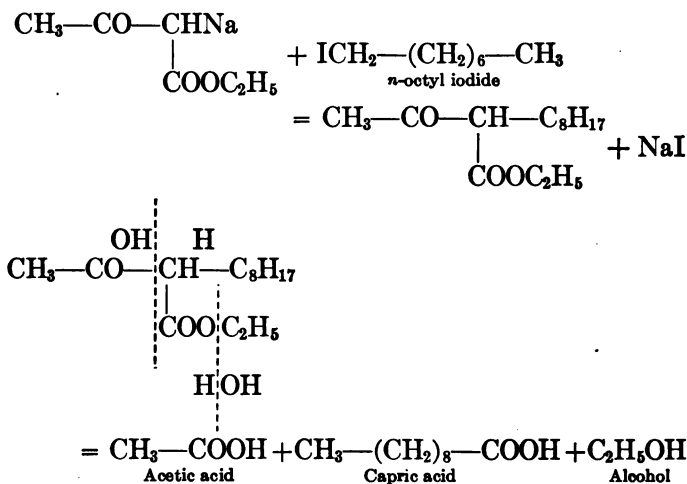
Aceto-acetic ester undergoes decomposition in two ways according to the conditions to which it is subjected. Dilute alkalis or acids on warming decompose it into a ketone, alcohol, and carbon dioxide. This is known as the *ketone decomposition (a)*. When it is decomposed by a strong solution of alcoholic potassium hydroxide the ester suffers *acid decomposition (b)*.



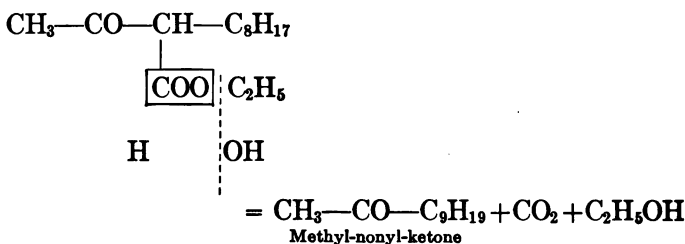
The great importance of aceto-acetic acid in synthesis lies in the fact that the sodium in sodio-aceto-acetic ester can be substituted by various radicals, after which the types of decomposition described above yield ketones or acids.

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Thus when sodio-aceto-acetic ester reacts with *n*-octyl iodide, the octyl group replaces the sodium. On acid decomposition this compound yields capric acid,  $C_{10}H_{20}O_2$ .

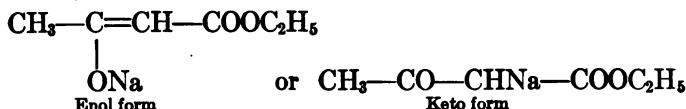


The same compound when subjected to the ketone decomposition yields methyl-nonyl-ketone:

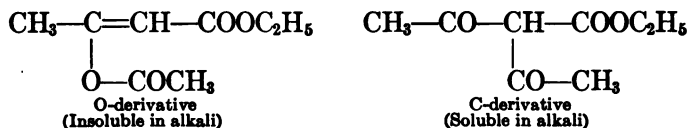


Numerous higher acids and ketones have been readily prepared by this reaction.

As was stated above, sodio-aceto-acetic ester may have either of two structures:



When an acid chloride reacts with sodio-aceto-acetic ester, it is possible to obtain at will a compound in which the acetyl group is linked directly to carbon or through oxygen to carbon.



When the sodio-aceto-acetic ester is treated directly with acetyl chloride, the C-derivative only is formed. This compound is soluble in alkali since the hydrogen in the CH group is linked to three negative radicals, two acetyl and one carbethoxyl groups. (Compare malonic ester.) When, however, the aceto-acetic ester is mixed with pyridine and the acetyl chloride added to the mixture, the O-derivative only is formed.

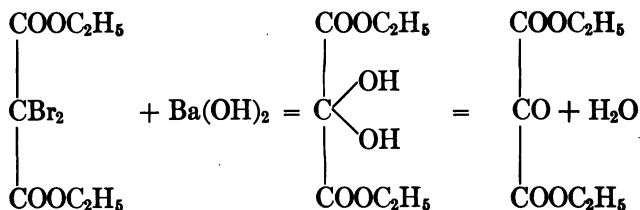
As a general rule the solubility in alkali of such derivatives as result from the condensation of halogen compounds with metallic compounds of substances which show tautomerism is accepted as evidence of the formation of the C type of derivative, since solubility in alkali should be expected where there is an active hydrogen atom which would permit the formation in alkali of a sodium or potassium derivative.

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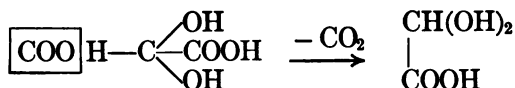
The study of a large number of such compounds has revealed some in which the change from the keto into the enol form or *vice versa* takes place slowly even in solution, and a few where one form is a solid and is stable except in solution. It has been found that the *enol* form gives an intense color reaction with ferric chloride and that the *keto* form does not. This serves as an easy test for identifying a tautomer.

### 128. Mesoxalic acid,

$\begin{array}{c} \text{COOH} \\ | \\ \text{CO} \\ | \\ \text{COOH} \end{array}$ 
 is formed when dibrom malonic ester is boiled with barium hydroxide solution, the two bromine atoms being replaced by hydroxyl groups:

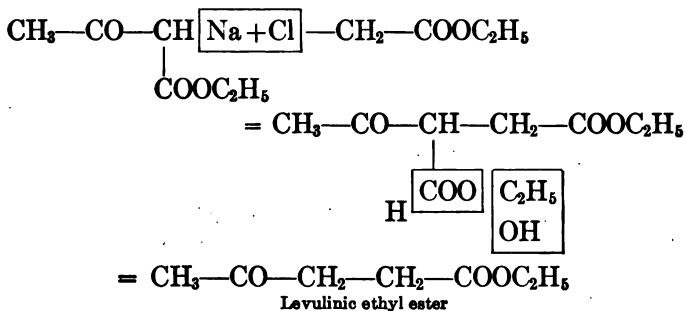


We have here another instance of the ability of one carbon atom to hold two hydroxyl groups when it is in close proximity to strongly negative radicals (compare glyoxylic acid and chloral hydrate). Mesoxalic acid is considerably more unstable than malonic acid, for on boiling with water it separates carbon dioxide and forms glyoxylic acid:



Mesoxalic acid is of biological interest owing to its relation to the formation of *alloxan* (140).

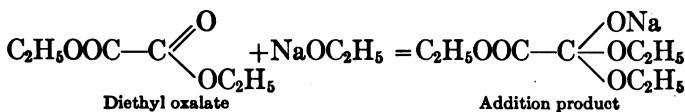
**129. Levulinic Acid**,  $\text{CH}_3\text{—CO—CH}_2\text{—CH}_2\text{—COOH}$ , is a  $\gamma$ -ketonic acid of interest because it is formed by the decomposition of sugars by means of strong hydrochloric acid. Its structure is revealed by its formation by the condensation of sodio-aceto-acetic ester with chloroacetic acid ester, followed by the ketone decomposition:

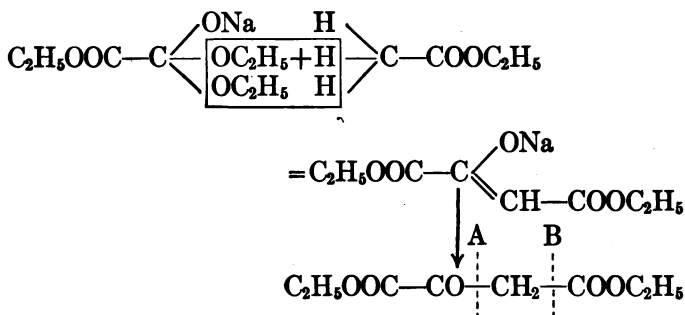


Levulinic acid is crystalline. It melts at  $33.5^\circ$  and boils with some decomposition at  $250^\circ$ . It behaves like the typical ketones in yielding an oxime, a cyanhydrin, and a hydrazone (37).

Levulinic acid when ingested in amounts above five to six grams is excreted unchanged in the urine.

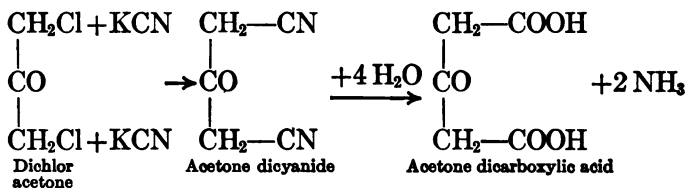
**130. Oxalacetic Acid** is obtained through the Claisen synthesis by the condensation of ethyl oxalate with ethyl acetate in the presence of sodium ethylate (127).





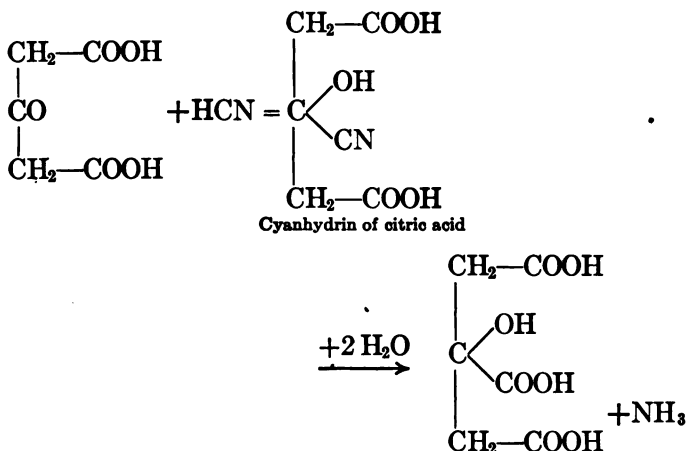
Like aceto-acetic ester oxalacetic ester can hydrolyze in two ways (127) at the points indicated by A and B. The first is accomplished by treatment with alkalis and yields oxalic and acetic acids; the second is effected by the action of dilute sulphuric acid and leads to the formation of pyruvic ester (67), carbon dioxide and alcohol.

**131. Acetone Dicarboxylic Acid**,  $\text{COOH}-\text{CH}_2-\text{CO}-\text{CH}_2-\text{COOH}$ , results from the nitrile formed by the action of potassium cyanide upon symmetrical dichloroacetone:

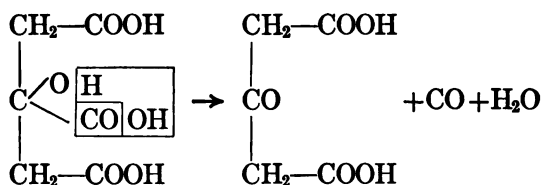


It is also formed by the action of strong dehydrating agents upon *citric acid*, a fact which gives a clue to the structure of the latter acid. Citric acid is formed from acetone dicarboxylic acid by the addition of hydrocyanic acid and subsequent hydrolysis of the oxynitrile.

**132. Citric Acid.**—As stated above, the nitrile of citric acid is formed by the cyanhydrin formation from acetone dicarboxylic acid :



The reverse reaction by which citric acid is converted into acetone dicarboxylic acid by dehydrating agents is as follows :



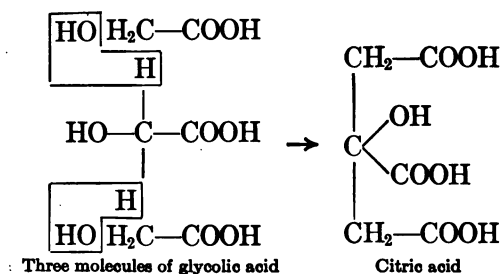
Citric acid occurs in the juice of many plants, especially in lemon juice, from which five per cent or more may be obtained, and in gooseberries, which contain about one per cent. It is also a normal constituent of the milk of



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animals, but it is not certain whether it comes from the food or is the product of the milk glands. It has also been detected in certain grains, and is therefore one of the most widely distributed compounds in nature. It crystallizes with one molecule of water in large colorless prisms. When it loses its water of crystallization through heating, it forms a fine white powder.

It is formed by the fermentative action of certain bacteria and molds, but the nature of the chemical process by which it is produced from sugars is not clear, since the sugars all contain the normal carbon chain whereas citric acid contains a branched carbon chain. It has been suggested that citric acid may result in fermentation by the condensation with loss of water from three molecules of glycolic acid:



## CHAPTER XII

### UNSATURATED DIBASIC ACIDS

#### *Maleic and Fumaric Acids and Their Isomerism*

133. There appears to be good evidence that two carbon atoms bound together by a single bond are able to rotate freely about their common axis. Thus only one ethylene chloride,  $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$ , is known. If free rotation of the carbon atoms in Figure 20 were not possible we should expect three modifications of this compound to exist:

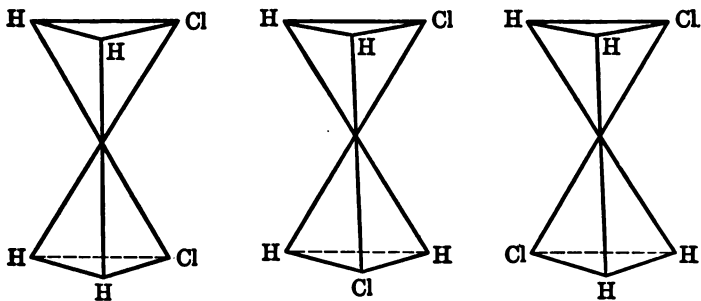


FIG. 20.

If, however, free rotation of the carbon atoms about their common axis is assumed, the three arrangements of the chlorine atoms represent phases of intramolecular movement and not stable positions of the tetrahedra. It is not necessary to assume a continuous movement

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of rotation. In fact we should expect that some one arrangement of the atoms would be more stable than any other, and that if the atoms were arranged in any way whatever they would return to the stable position and any movement within the molecule would constitute an oscillation about the stable position (82).

Such freedom of motion of one carbon atom with respect to another is in part lost when the double bond is

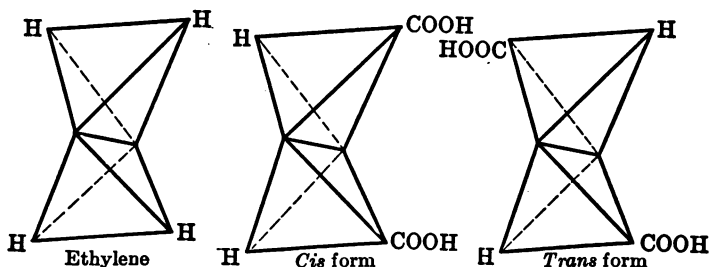


FIG. 21. — Maleic and Fumaric Acids.

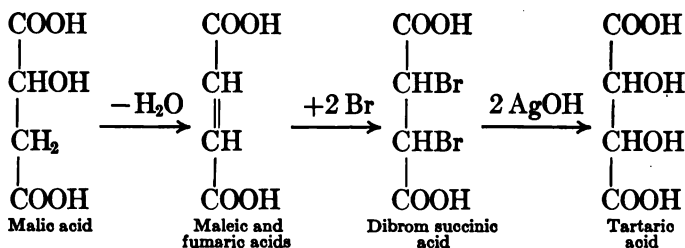
established, as was pointed out in discussing the isomerism of the crotonic acids (86). Assuming that in the case of the double bond the tetrahedra which represent the carbon atoms are in the position which is illustrated by their having one edge in contact, ethylene would be represented by Figure 21. In such a molecule we should expect two modifications of ethylene dicarboxylic acid:



The carboxyl groups may be arranged on the same or on opposite sides of the molecule. Since in compounds of

this type there is no asymmetric carbon atom, optical activity is not to be anticipated. Theory agrees with experience, which shows that fumaric and maleic as well as the crotonic acids (86) do not rotate the plane of polarized light.

Ethylene dicarboxylic acid results from malic acid (122) by the withdrawal of a molecule of water. Its relation to succinic and tartaric acids is shown by the following reactions:



The decision as to which of the configurations in Figure 21 is to be assigned to maleic and which to fumaric acid is determined by the following data: Both are produced from malic acid by splitting off water, but the conditions under which the reaction is effected determines the nature of the product. When the temperature of malic acid is raised to 140–150° and maintained there during 40 hours, fumaric acid is the principal product. When, however, the malic acid is contained in a distillation flask connected with a condenser and the temperature is quickly raised to 200°, there distills over the anhydride of maleic acid together with water.

Fumaric acid does not melt when heated, but sublimes.

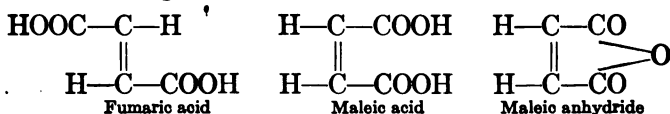
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It is but slightly soluble in water, 1 part dissolving in 148.7 parts at 16.5°. It does not form an anhydride which on taking up water regenerates fumaric acid, but when heated to the point of decomposition forms, along with considerable charring, maleic acid and its anhydride.

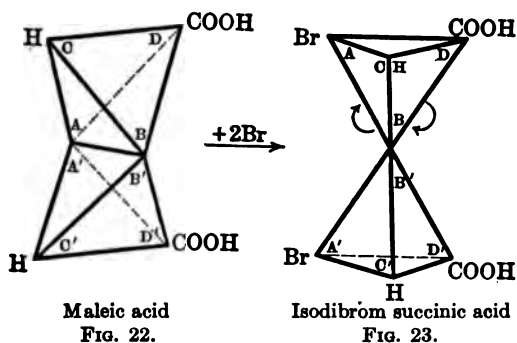
Maleic acid is soluble in 2 parts of water, at 1.0°. It readily forms an anhydride which takes up water, regenerating maleic acid. When maleic acid is heated in a sealed tube in aqueous solution to 210° it is converted partially into fumaric acid. Since both acids contain the same percentages of carbon, hydrogen, and oxygen, both absorb the same amount of halogen (2 atoms) and yield halogen-substituted succinic acids and both result from malic acid by the loss of one molecule of water, it is evident that their difference is a stereochemical one.

The dibrom succinic acids are not identical. That derived from fumaric acid is called dibrom succinic acid, and is but slightly soluble in water. That derived from maleic is called isodibrom succinic acid, and is much more soluble in water.

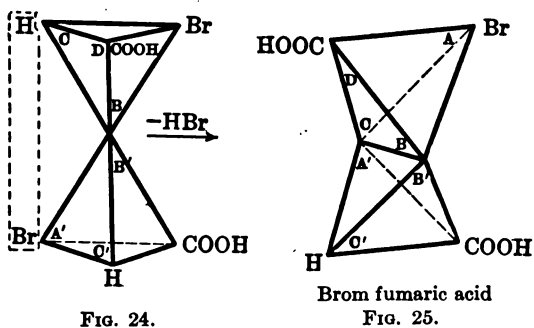
Since fumaric acid does not form an anhydride, it would appear that of the two possible positions which the COOH groups may occupy in Figure 21, the most probable one is that which separates them most. This separation should interfere with the abstraction of water from the two groups, and therefore to fumaric acid the *trans* structure has been assigned. Maleic is therefore the *cis* form.



Another interesting observation which confirms the belief in the structures assigned to these acids is the following: Both fumaric and maleic acids add two atoms of



bromine, but as stated above the dibrom addition products are not identical. The mechanism of this addition in the



case of maleic acid is made clear from an inspection of Figures 22-25.

The addition of bromine may take place at A and A' or at B and B'. In either case the same compound would

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result. If now in Figure 24 hydrobromic acid is separated from the isodibrom succinic acid, and a double bond again established, it must involve the rotation of the carbon atom represented by one tetrahedron through  $120^\circ$  in order to bring H and Br together. This, together with the folding of the two tetrahedra together, brings the two carboxyl groups into the *trans* position, and there results, from maleic acid, bromfumaric acid. In a perfectly analogous manner there should result from fumaric acid, by the addition of two bromine atoms, followed by the abstraction of hydrobromic acid, brom maleic acid. Experiment has demonstrated that by this process the *cis* and *trans* forms are transformed into the opposite isomer.

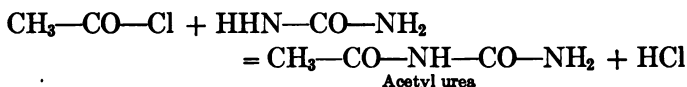
Fumaric acid occurs in nature in various plants. Maleic acid does not occur in nature. Fumaric acid serves as a source of energy for *Penicillium glaucum* and *Aspergillus niger*, while maleic acid is not utilized by these molds. Here we see another example of the fact which has been several times emphasized, that living organisms, being themselves constructed of complexes which exhibit the peculiarities of stereochemical configuration, show a decided preference for one isomer as contrasted with another as a source of nutriment.

## CHAPTER XIII

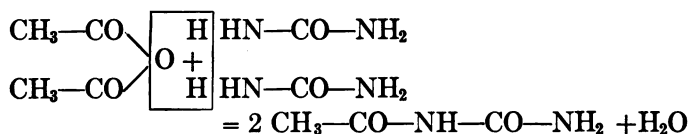
### THE UREIDES

#### *Ureides of the Monobasic Acids*

**134. Acetyl Urea.**—Urea, which was treated as the amide of carbamic acid (57) (amino formic acid) may also be regarded as a substituted ammonia in which a hydrogen atom of ammonia is replaced by  $\text{NH}_2\text{—CO}$ . Urea does in fact form a series of compounds in which it acts as does ammonia; thus it reacts with acid chlorides forming acetyl, propionyl, etc., ureas:



The same derivatives are formed by the action of urea on acid anhydrides:



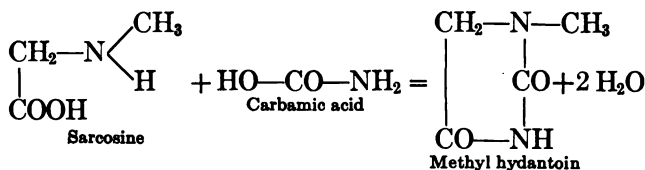
These compounds are solids. Acetyl urea forms silky needles melting at  $214^\circ$ . It is easily soluble in water and alcohol.

**Diacetyl Urea**,  $\text{CH}_3\text{—CO—NH—CO—NH—CO—CH}_3$ , is formed by the action of carbonyl chloride on acetamide:

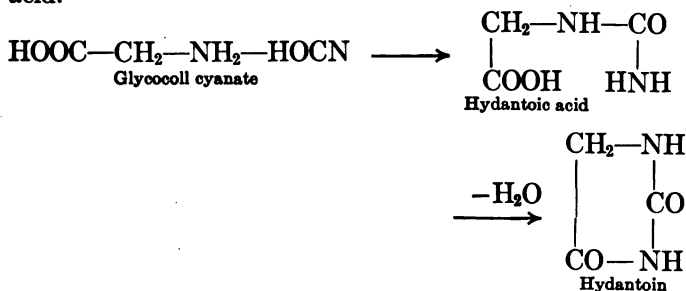




case to a considerable extent with the optical form not found in nature, or are completely burned to carbon dioxide, water, and ammonia. In the case of methyl-amino-acetic acid (sarcosine) (63) a part is combined with urea with the formation of methyl hydantoin, the latter appearing in the urine. The mode of formation is probably as follows:

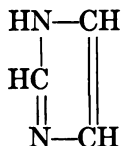


136. Hydantoin is formed by a method entirely analogous to the formation of urea from ammonium cyanate, by intramolecular rearrangement. Glycocoll (glycin) is capable of forming salts with acids. The glycocoll isocyanate, obtained by mixing glycocoll sulphate and potassium cyanate, when heated rearranges into hydantoic acid.



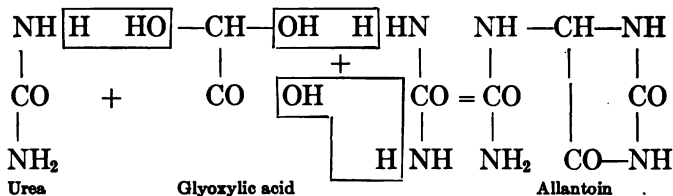
The mother substance from which hydantoin is derived may be regarded as glyoxaline:

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This ring structure is likewise referred to as *imidazole*. Hydantoin is a white crystalline compound which melts at 216°. The formation of substituted hydantoins results from the employment of amino acids other than glycocoll. These derivatives of the amino acids are in some cases compounds with much more favorable properties than the amino acids themselves, and serve a useful purpose in chemical work with these substances.

**137. Allantoin** is a urea derivative of hydantoin. It results from the condensation of two molecules of urea with one of glyoxylic acid. Glyoxylic acid (55), although it has the properties of both an acid and an aldehyde, always contains a molecule of water and appears to act as if it contained two hydroxyl groups linked to one carbon atom. The formation of allantoin is one of the reactions in which it displays this property.

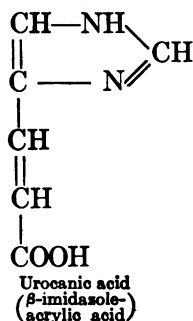
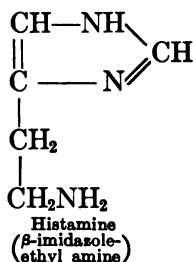
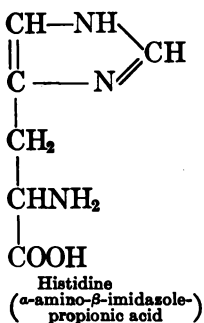


Allantoin is a constituent of various tissues of animals, occurring in small amounts. It is a constant constituent of the urine of various animals, much more in other

animals than in man. Allantoin is a crystalline compound having neither taste nor odor. Its solutions are neutral to litmus. It dissolves in 160 parts of cold water, but much more readily in hot water or hot alcohol. It melts with decomposition at 231°. It is precipitated by silver in ammoniacal solutions, but the precipitate is soluble in excess of ammonia. Lead, copper, and mercury likewise form insoluble compounds with it. It reduces Fehling's solution and is a disturbing factor in the employment of this reagent as a test for sugars in the urine.

On hydrolysis with acids or alkalies allantoin yields ammonia, carbon dioxide (from the urea complexes), and acetic and oxalic acids. Its identification is effected by its isolation as the silver compound, which contains 40.73 % of silver and by a positive qualitative test for oxalic acid after hydrolysis of a sample.

**138. Histidine.**—The glyoxaline or imidazol ring structure is present in one of the amino acids derived from the hydrolysis of many proteins, viz. *histidine*:



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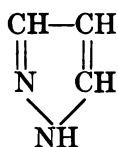
Histidine crystallizes in platelets which melt at  $253^{\circ}$  with decomposition. It dissolves readily in water, very slightly in alcohol, and not at all in ether. Its solution is alkaline to litmus. It forms salts with acids, the mono- and dihydrochlorides being of special importance in its isolation. It is precipitated from its solutions alkaline with sodium carbonate by mercuric chloride; by silver nitrate and ammonia or barium hydroxide; by mercuric sulphate in sulphuric acid solution; and by phosphotungstic acid.

Only l-histidine occurs in nature. It has a sweet taste. Putrefactive bacteria cause the elimination of carbon dioxide from it with the formation of *histamine*, or  $\beta$ -imidazole-ethylamine. While histidine itself is one of the essential amino acids which must be present in the food proteins, and can be introduced into the body without disturbance, histamine is a base which possesses most marked physiological action. Its action is primarily a stimulant effect on plain muscle. One part in 25 millions of Ringer's solution induces distinct contractions in a non-pregnant uterus. Larger doses induce tonic contraction.

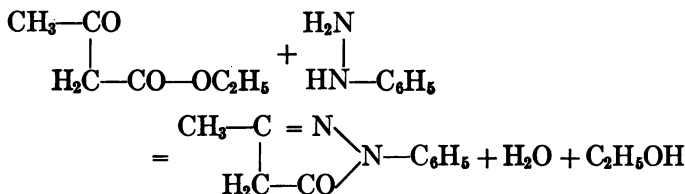
Histamine dihydrochloride,  $C_5H_9N_3 \cdot 2 HCl$ , is readily soluble in water, but sparingly in ethyl alcohol. It crystallizes in prisms which melt at  $140^{\circ}$ . The base forms a double salt with hydrochloro platinic acid which is soluble in hot water but very slightly soluble in alcohol. On boiling with bromine water histamine gives a claret color. It is precipitated by phosphotungstic acid, by ammoniacal silver solutions, and in alkaline solutions by mercuric chloride.

*Urocanic acid* or  $\beta$ -imidazole acrylic acid has been found in the urine of dogs, where it probably has its origin from histidine. It is not a normal constituent of the urine of the dog, but probably represents an abnormal type of metabolism.

**Pyrazole,**



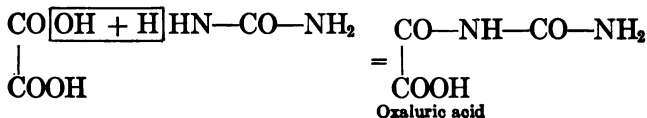
differs from imidazole in that the two nitrogen atoms in the ring are in position adjacent to each other. It is of importance in medicine because of its derivative, phenyl-dimethyl-pyrazolone, called antipyrine and phenazone. Methyl-phenyl-pyrazolone is formed by the action of phenyl hydrazine on aceto-acetic ester :



Antipyrine is formed in an analogous manner from methyl-phenyl-hydrazine.

*Ureides of the Dibasic Acids*

**139. Oxaluric Acid and Parabanic.**—Oxalic acid unites with urea with the separation of one molecule of water according to the following equation :

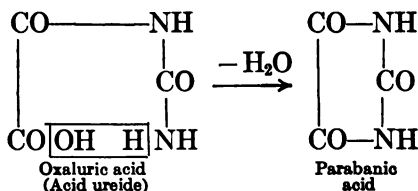


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This type of compound is known as *acid ureide*.

It is not found practicable to stop the condensation of oxalic acid and urea at this stage. Oxaluric acid may be prepared by the careful hydrolysis of parabanic acid.

A second molecule of water may be separated with the formation of a cyclic compound :

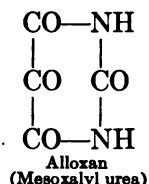
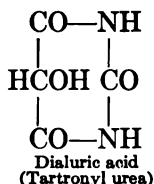
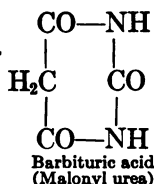


Parabanic acid is the simplest of the *ureides*.

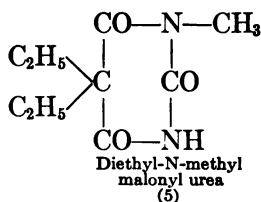
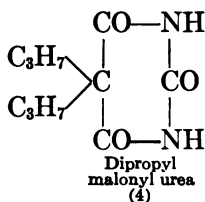
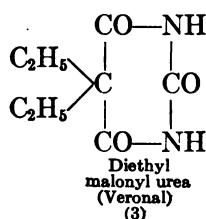
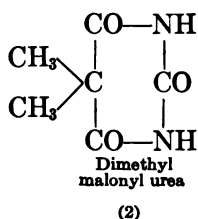
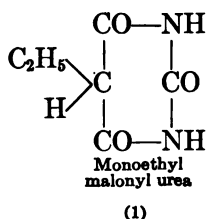
Oxaluric acid occurs in the urine in traces. It is a white crystalline compound soluble with difficulty in water. On warming with alkalis it is hydrolyzed to oxalic acid and urea.

Parabanic acid is likewise crystalline and is much more soluble than oxaluric acid. Parabanic acid is obtained by the oxidation of uric acid. Since its structure was understood from its synthesis from, and hydrolysis to, oxalic acid and urea it served to give a clue to the structure of the more complex uric acid molecule.

Ureides are also yielded by malonic, tartronic and mesoxalic acids. They are hydrolyzed to urea and the acids from which they were derived on boiling with acids or alkalis, the urea breaking down into ammonia and carbon dioxide. Their structures are illustrated by the following formulæ :



Malonyl urea is of special interest because of the narcotic effect of certain of its derivatives. The compound itself is without noticeable physiological action. Numerous derivatives have been prepared by substituting one or both hydrogen atoms of the malonyl group by alkyl and other groups. The following selected list will illustrate the remarkable influence which is exerted by certain groups as compared with others on the pharmacological action. Especially marked is the effect of accumulating alkyl groups, and the position occupied.

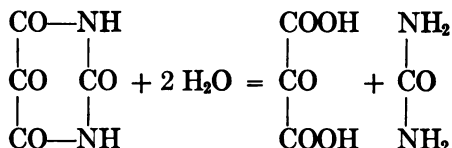




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When the derivatives (1) and (2) above were given to dogs weighing 6–8 kilograms, in doses of 3 to 4 grams, there was no noticeable effect. The diethyl derivative (3) in doses of 1–15 gm. induced deep sleep in about thirty minutes, lasting 24 hours. Of the dipropyl derivative (4) a 1-gram dose produced sleep after 30 minutes, lasting 48 hours, and 2 grams induced sleep within 15 minutes, and death. The toxic influence of introducing into diethyl urea (3) a methyl group linked to nitrogen as in (5) is very marked. A 1-gram dose induced sleep in 10 minutes which lasted two days and ended in death. Veronal and a few other similar compounds have found use as hypnotics.

**140. Alloxan**, or *mesoxalyl urea*, is formed from the oxidation of uric acid. On treatment with alkali it is hydrolyzed to mesoxalic acid and urea.

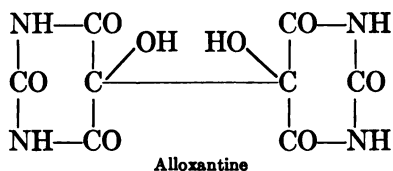


On boiling alloxan with dilute nitric acid it is oxidized to parabanic acid and carbon dioxide. This is an example of the transformation of a six-membered ring to one containing but five (**113**).

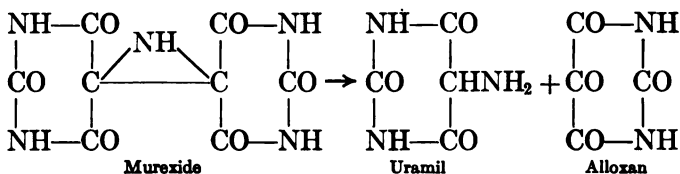
The formation of alloxan by the oxidation of uric acid served as further evidence as to the structure of a part of the molecule of that substance.

On reduction alloxan yields a derivative, alloxantine, containing two alcohol groups, which has double the molec-

ular weight of alloxan itself. The structure assigned to it is the following.



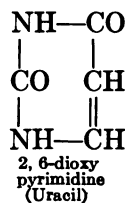
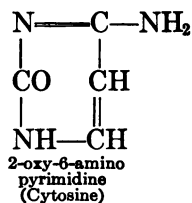
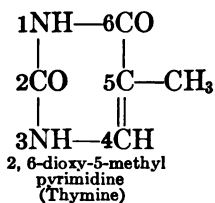
When alloxantine is treated with ammonia, it forms a salt-like derivative which is a purple-red dye called *murexide*. Murexide decomposes on hydrolysis into *uramil* and alloxan.



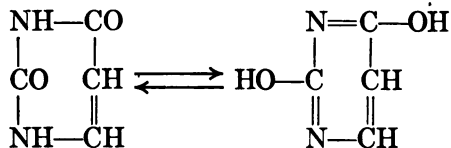
## CHAPTER XIV

### THE PYRIMIDINES, PYRAZINES AND PURINES

**141. The Pyrimidines.** In the nuclei of animal and plant cells occur the nucleic acids, complex compounds which on hydrolysis yield phosphoric acid, purines (147), pyrimidines, and a carbohydrate group (163). There have been found in nucleic acids three representatives of the pyrimidines :

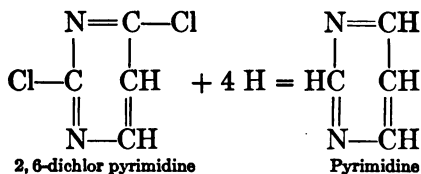


In the oxy pyrimidines there appears to be in the dissolved state a dynamic equilibrium between the molecules in which the oxygen is linked doubly to carbon, the *keto* form, with the enol form in which oxygen is singly linked to carbon and is in union with hydrogen forming a hydroxyl group :



## The Pyrimidines, Pyrazines and Purines 265

When, *e.g.*, uracil is acted upon by phosphorus oxychloride, the oxygen atoms are not replaced by two chlorine atoms, but chlorine replaces hydroxyl, and 2,6-dichlor pyrimidine results. This can be reduced to pyrimidine itself.



Thymine and cytosine are obtained from animal nucleic acids, and uracil and cytosine from plant nucleic acids.

**142. Thymine**,  $\text{C}_5\text{H}_8\text{O}_2\text{N}_2$ , is difficultly soluble in cold, but readily in hot, water, and slightly soluble in alcohol. It is precipitated by silver nitrate in the presence of a slight excess of ammonium or barium hydroxide, the precipitate being soluble in an excess of the alkalies. It is likewise precipitated by mercuric chloride and nitrate in the presence of sodium hydroxide. Phosphotungstic acid does not precipitate it, but it is readily carried down where other substances are precipitated by this reagent. Thymine sinters when heated quickly, at  $318^\circ$ , and melts with the evolution of gas at  $321^\circ$ .

**143. Cytosine**,  $\text{C}_4\text{H}_5\text{ON}_3\text{H}_2\text{O}$ , is soluble in 129 parts of water at  $25^\circ$ . It crystallizes from hot water in prisms which decompose with gas evolution at  $320^\circ$ – $325^\circ$ . The salts formed with sulphuric or hydrochloric acids are readily soluble, those with picric acid and hydrochloro-platinic acid difficultly soluble in water.

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Cytosine is precipitated by phosphotungstic acid (147), and by potassium bismuth iodide. It gives the Weidel reaction.

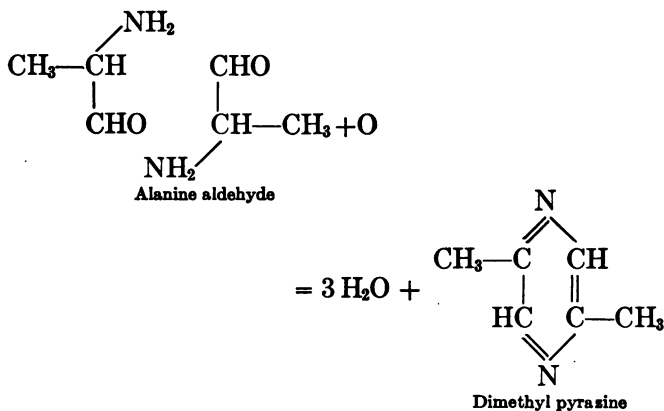
On treatment with nitrous acid it is converted into uracil. The mechanism of this transformation is the same as in the conversion of methyl amine into methyl alcohol (46). Here however there exists an equilibrium between the keto form usually written for uracil, and a small amount only of the enol form. The apparent replacement of the amino group by oxygen instead of by hydroxyl as in the primary amines is easily understood in the light of the behavior of urea and thiourea in the pseudo or iso form (56, 58) and of aceto acetic acid in the enol and keto forms (127).

**144. Uracil**,  $C_4H_4O_2N_2$ , is a white crystalline powder easily soluble in hot, difficultly soluble in cold, water. It dissolves readily in ammonia but scarcely at all in alcohol or ether. It is precipitated by mercuric nitrate, but not by phosphotungstic acid. It is precipitated under the same conditions as thymine by silver nitrate and ammonium or barium hydroxide. Uracil melts with decomposition at  $335-338^\circ$ . It likewise gives the Weidel reaction.

Numerous experiments in feeding animals with rations, all the constituents of which were known, have demonstrated that, although the nuclei of all cells yield at least two of the three pyrimidines just described, the diet need not contain any of these complexes. They can be synthesized in the animal body from certain of the amino acids yielded by the proteins of the food. The mode of formation of these compounds in the body is not understood.

PYRAZINE DERIVATIVES

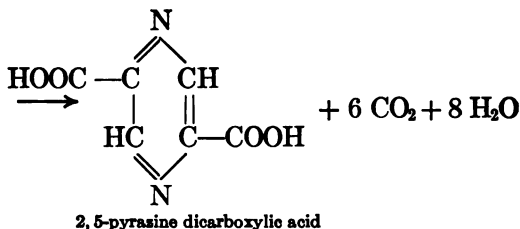
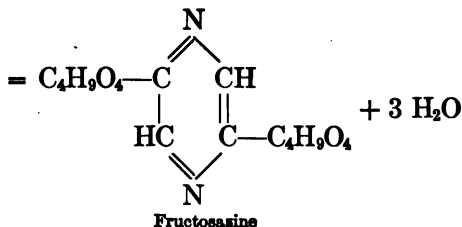
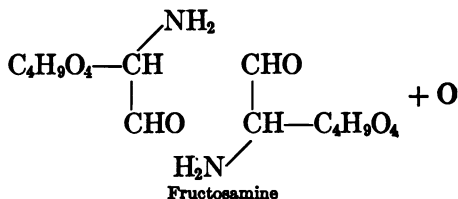
**145. Pyrazines.** The paradiazines are represented by several products of biological interest. Amino aldehydes, on oxidation, can condense to form substituted pyrazines. Thus :



Amino acids are not attacked by reducing agents, but their esters can be reduced to amino aldehydes by means of sodium amalgam.

An instance of the occurrence of such a condensation in the animal body is the elimination in the urine of 2,5-pyrazine-dicarboxylic acid after injection of d-fructose, a ketone sugar (156), and glycocoll into the veins of a rabbit. The mechanism of the reaction is easily understood. Fructose is known to combine with ammonia to form fructosamine. This compound is an amino aldehyde which condenses to the pyrazine ring; thereafter the sugar complex is oxidized to the last carbon atom, which is converted into a carboxyl group :

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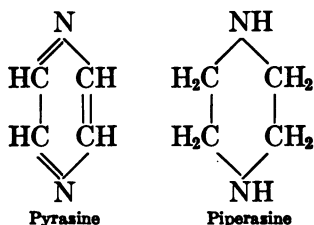


Fructosazine is oxidized outside the body by hydrogen peroxide with the formation of the same 2, 5-pyrazine dicarboxylic acid. The latter compound gives in neutral or faintly acid solution with ferrous sulphate a fine violet color which is easily seen in dilutions of 1 to 100,000 parts of water. By means of this reaction it has been shown that this pyrazine derivative when introduced into rabbits, even in small amounts, passes into the urine.

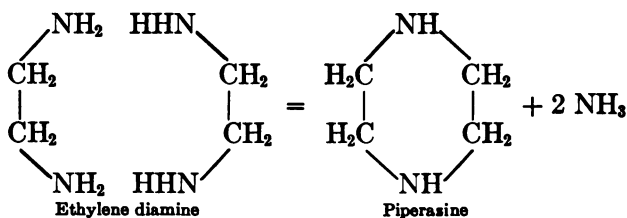
## The Pyrimidines, Pyrazines and Purines 269

The above condensation is of interest because it points to the possibility of the reaction of carbohydrates in the body with certain intermediary decomposition products of the amino acids with the formation of heterocyclic compounds, *i.e.* cyclic compounds containing more than one kind of element in the ring.

**146.** Piperazine differs from pyrazine in that the double linkages are eliminated by the addition of hydrogen or substituting groups, *i.e.* it is a *reduced* pyrazine.



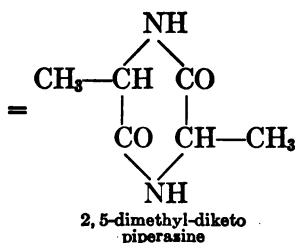
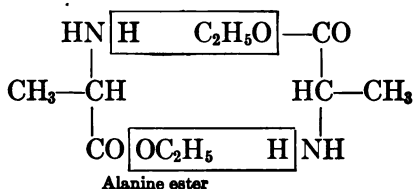
Piperazine is formed by heating the hydrochloric acid salt of ethylene diamine.



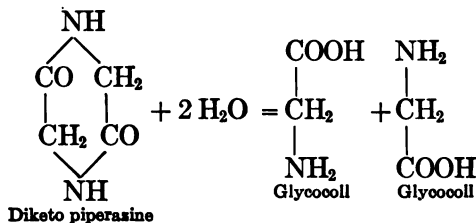
Esters of the amino acids change on standing, with the separation of alcohol, into their cyclic anhydrides, substituted ketone derivatives of piperazine. The change is accelerated by heating.



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These cyclic anhydrides have in many cases much more favorable properties for manipulation, as sparing solubility, etc., than have the amino acids themselves. On heating with acids they are hydrolyzed to the free amino acids.

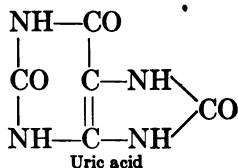


### THE PURINES

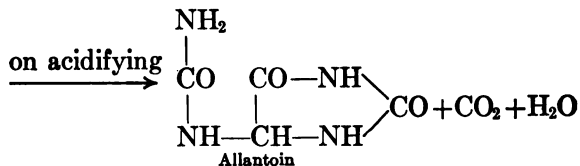
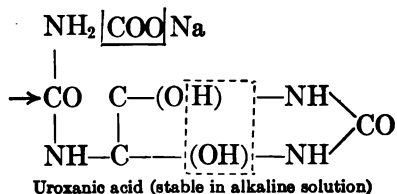
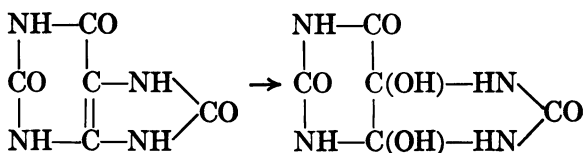
**147.** The researches of Emil Fischer on uric acid made clear the constitution of the group of compounds known as the purines. The constitution of uric acid was arrived at through the observation that on oxidation it yields

## The Pyrimidines, Pyrazines and Purines 271

*allantoin* (137). It contains therefore two urea groups in the molecule. The formation of parabanic acid and alloxan, whose structures are known from their formation from glyoxylic acid and urea, and mesoxalic acid and urea respectively, led to the proposal of the following structural formula :

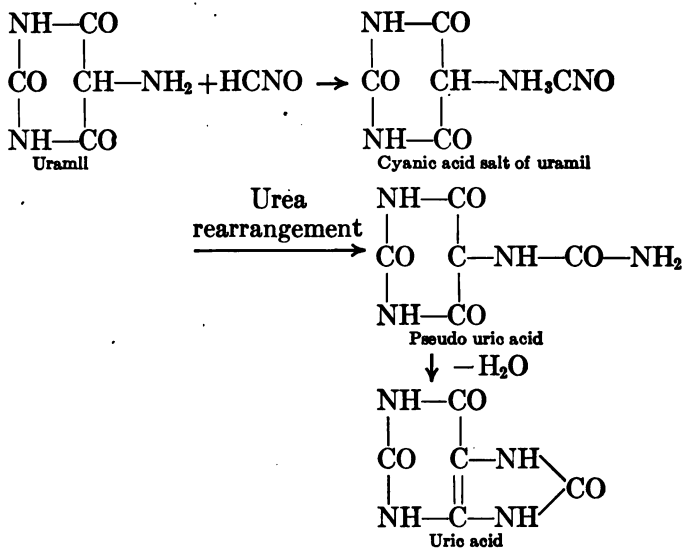


The formation of allantoin from uric acid, which takes place on oxidation with potassium permanganate in sodium hydroxide solution, may be regarded as proceeding through the following stages :



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Uric acid was synthesized in 1895 by Emil Fischer by the following series of reactions :



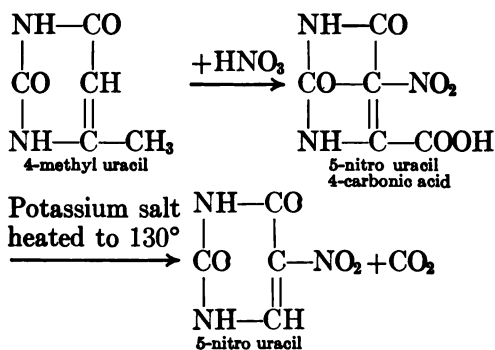
The second product in this series of reactions may be looked upon as a substituted ammonium cyanate. It should be expected therefore to rearrange on heating, into a substituted urea (urea in which one hydrogen atom is replaced by barbituric acid), and this is what happens. On heating this last product with oxalic acid it loses a molecule of water, passing into uric acid.

Uric acid is present in the urine of all animals. Among birds and reptiles the greater portion of the total nitrogen excreted is in the form of ammonium urate. Mammals excrete the greater part of their waste nitrogen as urea, only 1 per cent being eliminated as purines and this

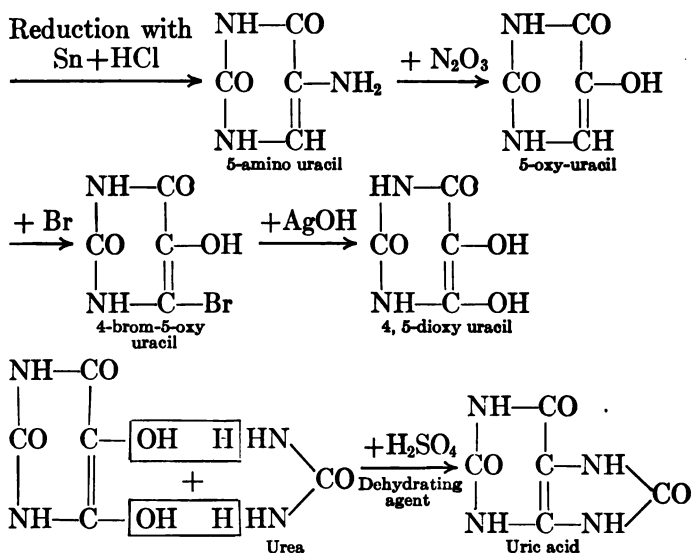
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mostly as uric acid and allantoin. Among mammals man occupies a peculiar position with respect to the excretion of uric acid. Studies of a considerable number of animals of diverse types have shown that the greater part of the purine nitrogen is eliminated in the form of allantoin. In man there is but a trace of allantoin excreted, practically all of the purine nitrogen appearing in the urine as uric acid. This finds its explanation in the fact that the reaction by which uric acid is transformed into allantoin, oxidation and hydrolysis, is catalyzed by a specific enzyme. This enzyme, which can be recognized in a tissue by its ability, under suitably regulated conditions, to destroy uric acid, is present in the tissues of all animals except man. In the absence of this catalytic agent the conversion of uric acid to allantoin goes on with extreme slowness.

Uric acid has been synthesized by a considerable number of methods starting from widely different materials. The early synthesis (1888) by Behrend and Roosen, which is particularly instructive, is illustrated by the following reactions:



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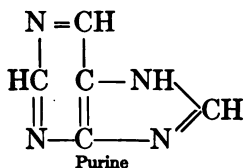
Uric acid is ordinarily prepared from urine. It exists in the urine in the form of the sodium and potassium salts, which are fairly soluble. One gram of dipotassium urate dissolves in 44 c.c. of water at room temperature, and 1 gram of disodium urate in 77 c.c. The free uric acid is soluble in about 4000 parts of water at room temperature. On adding hydrochloric acid to urine, to a distinctly acid reaction, uric acid crystallizes out usually arranged in sheaves, and greatly pigmented. By dissolving in strong sulphuric acid (35 %) and diluting with water the acid crystallizes out and may thus be purified.

Uric acid acts like a dibasic acid, forming two series of salts, acid and neutral urates. The ammonium, calcium, and barium salts are more difficultly soluble than are those

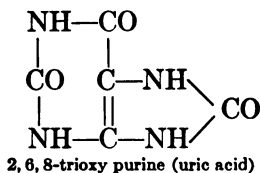
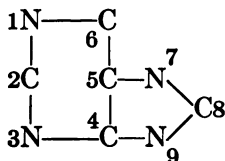
## The Pyrimidines, Pyrazines and Purines 275

of the alkalis. Phosphotungstic acid precipitates uric acid completely, as does also silver nitrate in ammoniacal solution in the presence of magnesium salts. Cuprous oxide (copper sulphate in the presence of sodium acid sulphite) forms an extremely insoluble compound with uric acid and also with purine bases. The acid character of uric acid is due to the existence in solution of the tautomeric *enol* form in dynamic equilibrium with the *keto* form which is illustrated by the usual structural formula. That the reactive form of uric acid is represented by the *enol* formula is shown by the fact that when phosphorus oxychloride acts on uric acid, OH is replaced by one chlorine, whereas if the reaction took place between the chlorinating agent and oxygen doubly linked to carbon, oxygen should be replaced by two chlorine atoms (32).

The mother substance of uric acid and of a series of biologically important purine bases is purine:

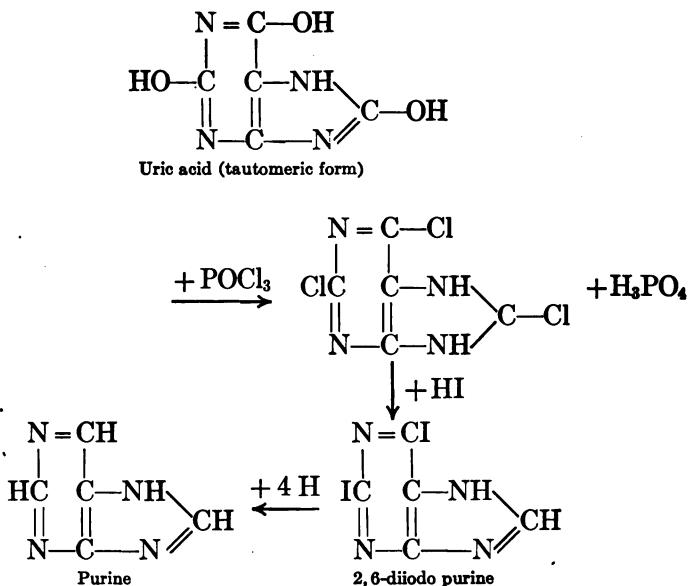


The order of numbering the atoms in the purine nucleus for indicating the position of substituted purines is as follows:



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Purine is formed from trichlor purine, which results directly from the action of phosphorus oxychloride on uric acid.

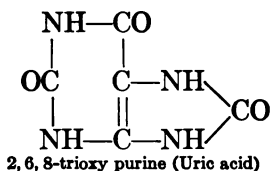
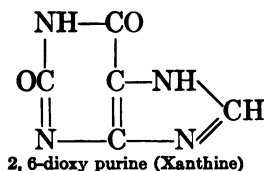
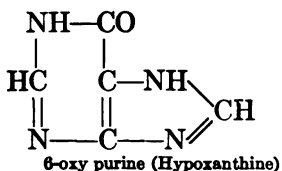


The urea complexes behave in these reactions as if they had the *iso* structure (57, 58).

**Purine** is a crystalline substance which melts at 211–212°. It is a basic compound and forms salts with various acids.

**Hypoxanthine**, C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O.—There are besides uric acid two other oxypurines which are of great biological interest, viz. xanthine and hypoxanthine. Their relation to uric acid is shown by their formulæ:

## The Pyrimidines, Pyrazines and Purines 277



Hypoxanthine is a crystalline compound soluble in 69.5 parts of boiling water and in 1400 parts at 19°. It dissolves readily in mineral acids and alkalis. It is insoluble in alcohol. The hydrochloride,  $\text{C}_5\text{H}_4\text{N}_4\text{O} \cdot \text{HCl} + \text{H}_2\text{O}$ , is decomposed on crystallization from water, but can be crystallized from concentrated hydrochloric acid. The sulphate and nitrate are likewise decomposed by water. Hypoxanthine picrate is a characteristic salt. Hypoxanthine is precipitated from its solutions by ammoniacal silver nitrate.

Hypoxanthine is found in the muscles and organs of the animal body and is accumulated in beef extract. It is likewise widely distributed in plants.

Xanthine,  $\text{C}_5\text{H}_4\text{N}_4\text{O}_2$ , is likewise found in animal tissues and widely distributed in plants. It is very slightly soluble in water, about 1 to 14,000 parts at 16°, and in 1400 parts of boiling water. It dissolves more readily in alkalis. Xanthine, like hypoxanthine, forms salts with acids. However, it also forms crystalline compounds with alkalis.



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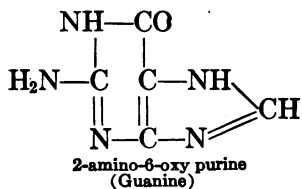
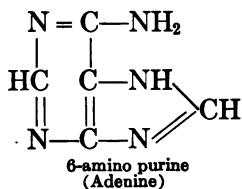
On evaporation with concentrated nitric acid, there remains a yellow residue, which on treatment with sodium hydroxide becomes reddish yellow and on heating purple-red. This is a modification of Weidel's reaction.

### AMINO PURINES

**148. Adenine**,  $C_5H_5N_5$ .—There is but one amino purine found in nature, viz. 6-amino purine or adenine. It is a product of the hydrolysis of nucleic acids of both plant and animal origin. It is crystalline and decomposes at  $360-365^\circ$ . It is soluble in 155 parts of water at  $18^\circ$ . It forms salts with mineral acids which in contrast to those of hypoxanthine and xanthine can be crystallized from water. Its oxalate and picrate are characteristic salts. The latter serves to separate adenine from hypoxanthine.

Adenine does not give the xanthine or murexide tests. It is best prepared from extracts of tea leaves.

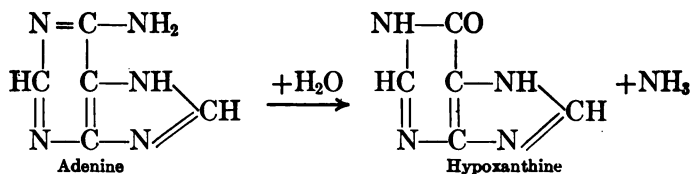
Adenine is usually associated with the closely related purine base guanine, or 2-amino-6-oxy purine.



**Guanine** is found widely distributed in both animal and plant tissues, and is present in nucleic acids. It is the principal constituent of the excrement of spiders, and is occasionally found deposited as crystals in the joints of swine in the so-called "guanine gout." Guanine is

## The Pyrimidines, Pyrazines and Purines 279

insoluble in water, alcohol, and ether, very slightly soluble in ammonia, but readily soluble in sodium hydroxide. On the addition of copper sulphate and sodium bisulphite to its solutions the cuprous oxide compound of guanine is precipitated quantitatively. With acids it forms salts which crystallize, but these are stable only in the presence of an excess of the acid. In water they are decomposed. The metaphosphate, picrate, and silver nitrate compounds are useful in its isolation and purification. Adenine and guanine are the only purines which are present in the nucleic acid molecule. In the body they react with water through the catalytic agency of enzymes, which accelerate the change, forming oxypurines, from adenine, hypoxanthine, and from guanine, xanthine:



This transformation also occurs through the action of nitrous acid on adenine, the amino group being replaced by hydroxyl, which passes in part into the keto form. Hypoxanthine can take up an atom of oxygen, being converted into xanthine; and xanthine can in like manner be oxidized to uric acid. These deaminations and oxidations represent the course of purine metabolism in the body. Guanine is hydrolyzed to guanidine, etc. The enzymes which effect these changes in measurable time are specific in character. Thus there is an *adenase* which can deam-

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*inize* adenine to hypoxanthine, and a *guanase* which catalyzes the transformation of guanine into xanthine as described above. Not all tissues contain all the enzymes necessary to the transformation of the amino purines into oxypurines. Thus adenase is not found in the tissues of the rat. Guanase is absent from the spleen and liver of the pig and from the human spleen, but is present in most other tissues. The enzyme which accelerates the oxidation of hypoxanthine into xanthine is called *hypoxanthine-oxidase*; that which oxidizes xanthine to uric acid is called *xanthine-oxidase*. The enzyme which accelerates the oxidation of uric acid to allantoin is called *uricase*. The ending *ase* is employed to designate enzymes or organic catalysers.

The nucleic acids of both animal and plant origin contain but two purines, adenine and guanine. The hypoxanthine, xanthine, and uric acid found in the tissues are formed by the deamination and oxidation of these.

Within recent years feeding experiments with young animals have shown that with diets entirely free from any of the purines, growth and hence the synthesis of nucleic acids can take place at the normal rate. Such animals regularly excrete uric acid. There is no doubt that in such experimental animals adenine and guanine are produced synthetically. The substances from which purines are formed in mammals are not known with certainty, but experiments with birds make it highly probable that they are urea, ammonia, and lactic acid. In birds the seat of synthesis of uric acid is the liver. When the liver of a bird is excised the bird has been found to

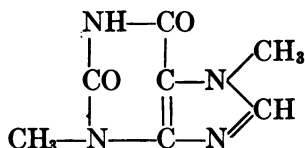
## The Pyrimidines, Pyrazines and Purines 281

excrete, during the few hours it can live, ammonia and lactic acid instead of uric acid.

### THE METHYL PURINES

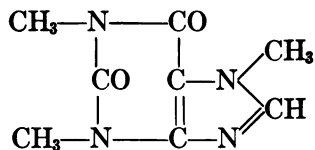
149. Aside from the purines ingested as adenine and guanine or their degradation products there occur in plant foods two important methylated purines, theobromine and caffeine.

**Theobromine** is 2,6-dioxy-3,7-dimethyl purine :



Occurs in the cocoa bean, and is found in chocolate to the extent of 1 to 2 per cent. It is a dimethyl xanthine. It is a white crystalline powder, soluble in ether, insoluble in alcohol and water, but somewhat soluble in hot chloroform. It forms crystalline salts with strong acids, but these are decomposed into the base and acid by water. It sublimes unchanged at 290°. It is a powerful diuretic and nerve stimulant. It has a bitter taste. The hydrochloride and salicylate are also much employed.

**Caffeine** is 2,6-dioxy-1,3,7-trimethyl purine :



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It occurs in tea and coffee, guarana, and in kola nuts. Coffee contains about one per cent. It is soluble in 80 parts of water; 55 parts of alcohol, 7 parts of chloroform, and 555 parts of ether at 15°. Caffeine crystallizes from water in white fleecy masses of silky needles, having a bitter taste. It sublimes at 178°.

Caffeine is a diuretic and cerebral stimulant and has a pronounced stimulating action on the heart.

In passing through the body caffeine and theobromine are partially demethylated, and they appear in the urine to some extent as monomethyl and dimethyl purines. In part the methyl groups are completely removed, the nucleus being excreted as uric acid.

## CHAPTER XV

### THE CARBOHYDRATES

150. There is found in nature a large group of compounds to which the general name *carbohydrates* is applied. These are either aldehyde alcohols or ketone alcohols, or are converted into aldehyde alcohols or ketone alcohols on hydrolysis. The carbohydrates include the sugars, starches, celluloses, gums, pectins, etc. In many of them the composition corresponds closely to the general formula  $C_n(H_2O)_n$ , or one molecule of water to each carbon atom. Thus, cane and beet sugar have the formula  $C_{12}H_{22}O_{11}$  which corresponds to  $C_1 11(H_2O)$ ; glucose and fructose,  $C_6H_{12}O_6 = C_6 6(H_2O)$ ; starch, the molecule of which is very large, corresponds to the formula  $C_6 5(H_2O)$ . It was from this relationship that they received the name carbohydrate. There are several representatives of the carbohydrates which do not conform to this formula; and there are on the other hand a number of compounds totally unrelated chemically to the carbohydrates which contain carbon, hydrogen, and oxygen, the two latter elements in the proportion to form water. As examples may be cited formaldehyde,  $CH_2O$ , acetic acid,  $C_2H_4O_2$ , and lactic acid,  $C_3H_6O_3$ . The carbohydrates are of the greatest importance as a source of energy to the animal body, and as a rule among the herbivora and omnivora they constitute

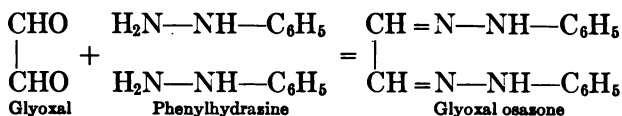
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the greater part of the diet. In man there frequently occurs a pathological state (diabetes) in which the body is incapable of oxidizing carbohydrates, the absorbed sugars, wholly or in part, being eliminated unchanged in the urine. The exact nature of this disorder is not understood, and it is therefore of the first importance that we should have a full understanding of the chemical nature of the carbohydrates and of the changes which they undergo in the course of normal metabolism.

The classification of the carbohydrates is based upon the fact that there are found widely disseminated in nature certain aldoses and ketoses which contain six carbon atoms, called hexoses (glucose, fructose, etc.) and others called polysaccharides (starches, dextrine, cellulose, etc.) which are polymers of the hexoses and yield the latter on hydrolysis. Widely prevalent also are the pentosans, polysaccharides which on hydrolysis yield aldopentoses, or sugars containing five carbon atoms. The four aldohexoses and five aldopentoses are all aldehydes and in addition contain alcohol groups. Between these pentoses and hexoses, which are termed monoses, and their complex polymers, are the disaccharides, trisaccharides, etc., yielding on hydrolysis two, three, etc., molecules of monoses. The term sugar is usually applied only to mono-, di-, and trisaccharides.

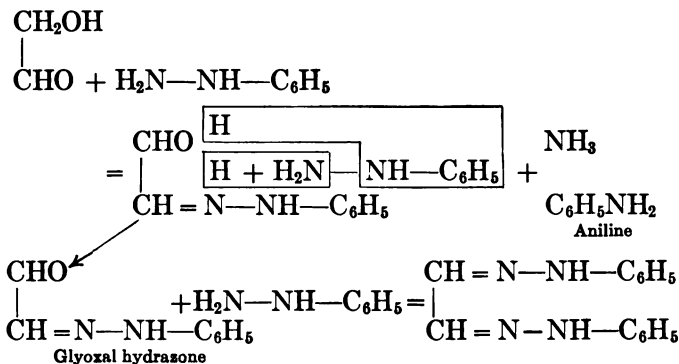
Before discussing the chemistry of the carbohydrates it is necessary to describe in further detail the behavior of phenylhydrazine with several types of compounds. The reaction of hydrazine,  $\text{NH}_2\text{—NH}_2$ , and its derivatives with aldehydes and ketones has already been pointed out

(32, 37). With compounds of the type of acetaldehyde or acetone, mono derivatives, *hydrazones*, are formed. With glyoxal, phenylhydrazine reacts to form a dihydrazone, or *osazone*.



The same osazone is obtained by the action of phenylhydrazine upon glycolaldehyde, the simplest of the carbohydrates.

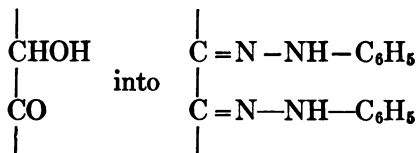
The reaction with glycolaldehyde takes place in three stages, in one of which a *hydrazone* is formed, in the second the adjacent carbinol group is converted by the withdrawal of two hydrogen atoms into carbonyl, with the destruction of a molecule of phenylhydrazine. In the third step another molecule of phenylhydrazine is condensed with the newly formed carbonyl group producing the osazone.





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This conversion of the group

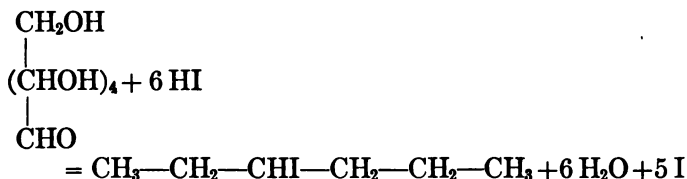


is characteristic of the action of phenylhydrazine on the simple carbohydrates, and indicates that a secondary alcohol group is attached to the carbon atom adjacent to the aldehyde group.

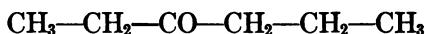
The observation of the formation of osazones by the sugars made possible the ready separation and purification of sugars. The difficulties attending the crystallization of sugars from their solutions, owing to their great solubility and tendency to form sirups, had previously prevented rapid advance in the study of the chemistry of the carbohydrates. The osazones are difficultly soluble in water, crystallize well, and have definite melting points. The latter property makes it easy to identify the individual sugars.

The aldohexoses all have the formula  $\text{C}_6\text{H}_{12}\text{O}_6$ . They all react with phenylhydrazine in the manner described above, showing that they contain the aldehyde group and a hydroxyl in the alpha position to it. Their aldehyde property is further shown by the fact that they exert a reducing action on certain salts of the heavy metals, as alkaline copper and bismuth solutions and ammoniacal silver solutions. They are reduced by nascent hydrogen to hexahydric alcohols, and are oxidized to pentahydroxy acids containing six carbon atoms.

All the aldohexoses contain a *normal carbon chain*. This is shown by the fact that on reduction with hydriodic acid they yield a *n*-secondary hexyl iodide.



This iodide can be converted into a secondary alcohol by ordinary methods (13, 22) and has been shown to yield on oxidation ethyl, propyl ketone :



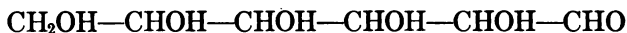
which is oxidizable to acetic, propionic and butyric acids (38).

The presence of five hydroxyl groups is further established by the fact that the aldohexoses react with acetic anhydride to form penta acetyl derivatives (52). When the latter are purified and a weighed sample saponified with standard alkali, it is found that the acetic acid formed corresponds with the theoretical amount for such compounds.

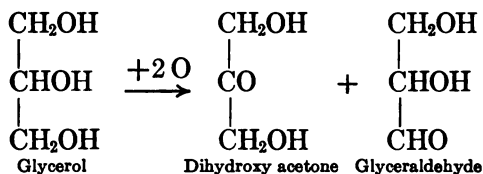
Since two hydroxyl groups can remain linked to a single carbon atom only in special cases when the latter is in close proximity to one or more strongly negative radicals (32, 55), none of which exist in the sugar molecule, it is assumed that the carbon atoms other than that contained in the aldehyde group each hold a single hydroxyl, since the hypothesis that certain carbon atoms have linked to them

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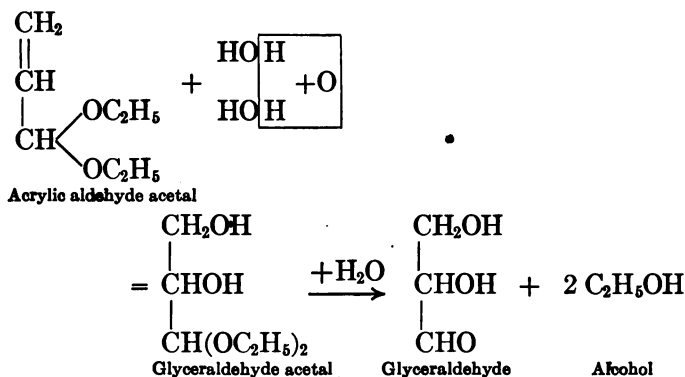
more than one hydroxyl is untenable. Each one except the end ones must be linked on two sides to carbon and on one to hydroxyl. The remaining bond must be occupied by hydrogen. By such reasoning we arrive at the conclusion that the structure of the aldohexoses is the following :



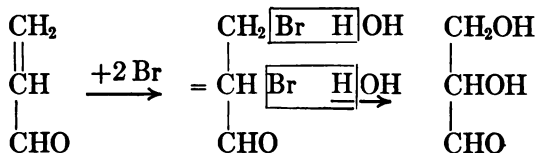
**151. Methods of Synthesis of the Monoses.** — 1. By the carefully regulated oxidation of the polyatomic alcohols. As an example may serve the oxidation of glycerol. It has previously been described (36) how by cautious oxidation of this triatomic alcohol there results glyceraldehyde, which in the terminology of the carbohydrates is glycerose. The chief product of this reaction is always the isomer dihydroxy acetone :



Glyceraldehyde can be prepared free from dihydroxy acetone by the oxidation of acrolein (86), the aldehyde group of the latter being protected during the process by first converting it into the acetal (32). As in the case of the fatty acids, oxidation of compounds containing doubly linked carbon leads first to the formation of hydroxy groups at this point.

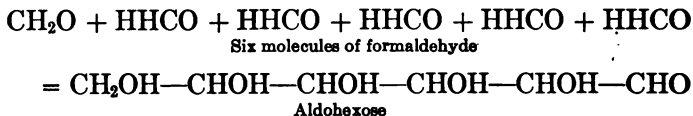


2. By hydrolysis of brom aldehydes with barium hydroxide. Mention has already been made of the formation of glycol aldehyde from brom acetaldehyde by this method (35). By this method glyceraldehyde may also be prepared. Starting with acrylic aldehyde, two bromine atoms are added. The dibrom propyl aldehyde reacts with water when heated with barium hydroxide, the bromine atoms being replaced by hydroxyl.



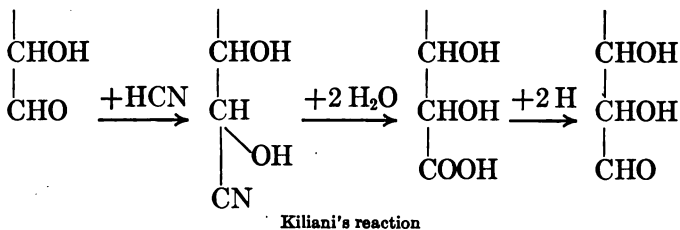
3. When formaldehyde is treated with weak alkali (limewater) it condenses to a mixture of compounds of the formula  $\text{C}_6\text{H}_{12}\text{O}_6$ . The mixture is sirup-like and sweet. It has received the name *formose*. In its formation six molecules of formaldehyde condense to form a mixture of aldohexoses :

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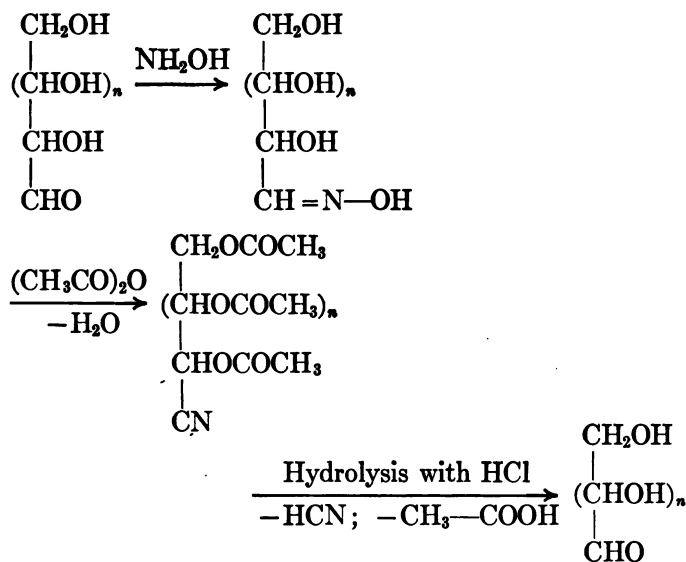
4. Dilute alkalies cause two molecules of glyceraldehyde to condense, forming an aldohexose. It is called *acrose*. Like synthetic compounds in general the hexoses formed by the methods just described are optically inactive, whereas all the sugars found in nature exhibit optical activity.

5. A most important method discovered by Kiliani makes possible the building up of tetroses from trioses, hexoses from pentoses, etc. It consists in the addition of hydrocyanic acid to the aldehyde group of the pentose, forming an oxynitrile, in a manner analogous to the formation of lactic acid from acetaldehyde (66). The nitrile radical is hydrolyzed to a carboxyl group. This in solution forms a lactone with the hydroxyl in the  $\gamma$ -position (125), and the lactone can be reduced by means of nascent hydrogen (sodium amalgam) to an aldehyde.



6. Wohl discovered a method which makes possible the reversal of the preceding operation (Kiliani's reaction) and the formation of a sugar molecule having one less

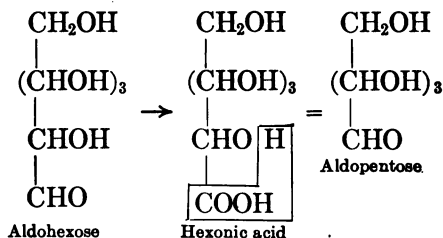
carbon atom in the molecule than is contained in the sugar employed to begin with. It involves (1) the formation of an aldoxime by the condensation of hydroxylamine with the aldehyde group (32). (2) The oxime is treated with acetic anhydride and sodium acetate which abstracts the elements of a molecule of water from the oxime, forming a nitrile (40). Incidentally the acetyl derivatives of the hydroxyl groups are produced. (3) Potassium hydroxide removes the acetyl radicals by hydrolysis, and on subsequent treatment with hydrochloric acid hydrocyanic acid is split off with the formation of an aldehyde group. The reactions will be made clear by the following scheme :



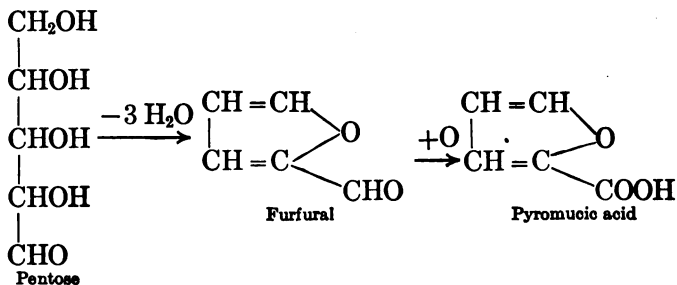
Wohl's reaction

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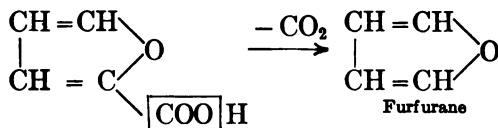
7. It has also been found that when a simple sugar, as an aldohexose, is oxidized carefully, the first product of the reaction is an acid having the same number of carbon atoms. On further oxidation of the calcium salt of this with hydrogen peroxide in the presence of a little ferric acetate which acts as a catalytic agent, carbon dioxide is separated and the alcohol group which in the sugar occupied the  $\alpha$ -position to the aldehyde group is oxidized to aldehyde. There results the aldo sugar having one less carbon atom than that employed in the oxidation.



The pentoses are readily distinguishable from the hexoses by their tendency to lose three molecules of water and pass into furfural, a cyclic aldehyde containing four carbon atoms and one oxygen atom in its ring.



The structure of furfural is evident from (1) its mode of formation, (2) its conversion into an acid, pyromucic acid,  $C_4H_5OCOOH$ , on oxidation, (3) the formation of *furfurane* by the loss of carbon dioxide



on heating in a sealed tube to  $275^\circ$ . That furfurane has its oxygen in the ring and not in the form of a carbinol or carbonyl group is shown by the fact that with metallic sodium no hydrogen is evolved, as is the case with the alcohols (15), and it does not react with hydroxylamine or other reagents with which aldehydes or ketones condense. Furfural is an oily liquid with an agreeable odor which boils at  $162^\circ$ . With paper moistened with aniline acetate it gives an intense red color.

Those carbohydrates which contain an aldehyde group are called *aldoses*, and those which contain a ketone group *ketoses*. The names of the sugars end in *ose* and those of the alcohols which result from the reduction of the carbonyl group end in *ite*. Glycol aldehyde and glycerose, while chemically sugars, do not occur in nature except possibly as unstable, transitory, intermediary products of the oxidation of the carbohydrates. They are not named in accordance with the systematic nomenclature of the sugars. Since every representative of this group of sub-

stances contains in addition to the *carbonyl* group  $\begin{array}{c} | \\ \text{C}=\text{O} \\ | \end{array}$



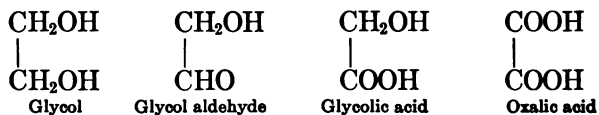
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(aldehyde or ketone group) at least one *carbinol* group

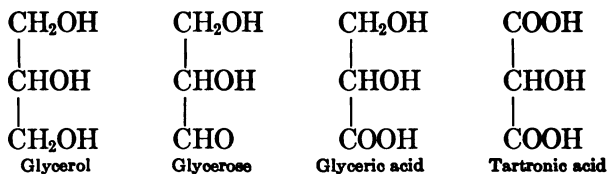
HCOH, it must follow that for each of the aldoses, there

are two acids which can be derived by oxidation and an alcohol which can be obtained by reduction. The following résumé of the simple aldoses, together with the corresponding alcohols and acids, will serve to illustrate their relationships :

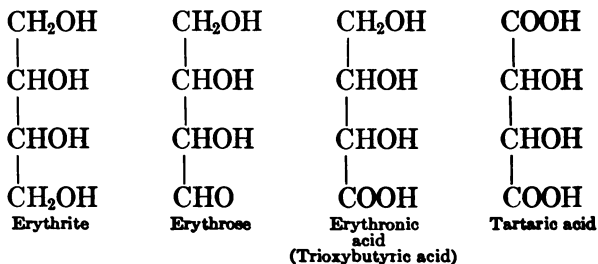
### Diose, $C_2H_4O_2$



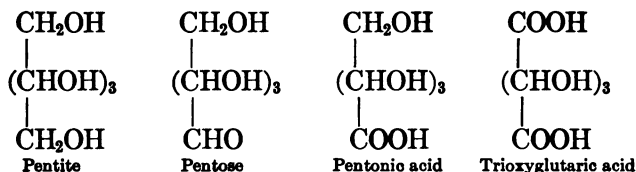
### Triose (glycerose), $C_3H_6O_3$



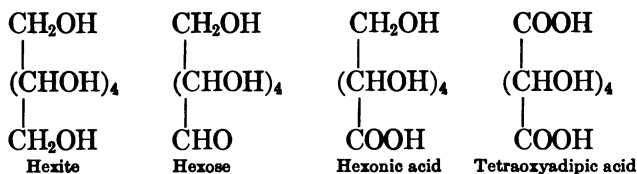
### Tetrose (erythrose), $C_4H_8O_4$



Pentose (xylose, arabinose, etc.)



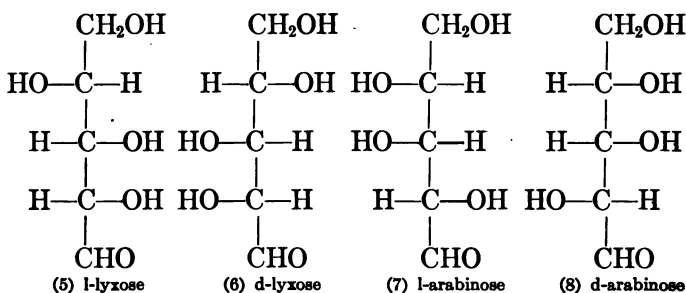
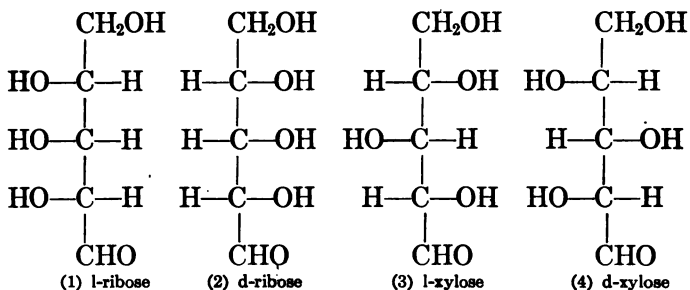
Hexose (glucose, mannose, galactose, etc.)



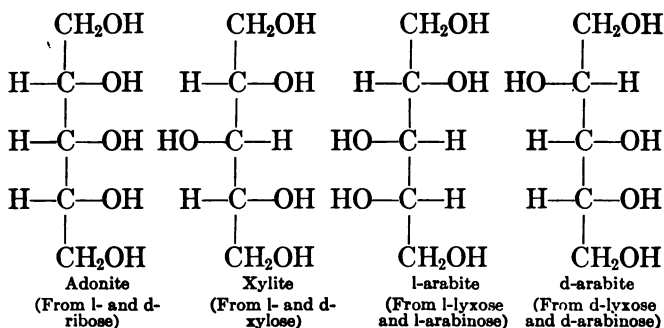
Glycol has no carbon atom possessing asymmetry and therefore shows no optical activity. All the other aldoses possess one or more asymmetric carbon atoms and therefore exist in two or more isomeric forms. Glycolaldehyde is an unstable substance and has never been isolated from plant or animal tissues. The same is true of glyceraldehyde. Both of these are known through the synthetic products only.

A tetrte, inactive erythrite (i-erythrite) is found free in the Alga, *Protococcus vulgaris*. Tetroses have never been found in nature, but have been prepared synthetically. There are theoretically possible twelve isomeric aldopentoses, viz., an optically inactive, a dextro- and a levorotatory form of each of the four possible aldopentoses, whose formulæ are illustrated as follows :

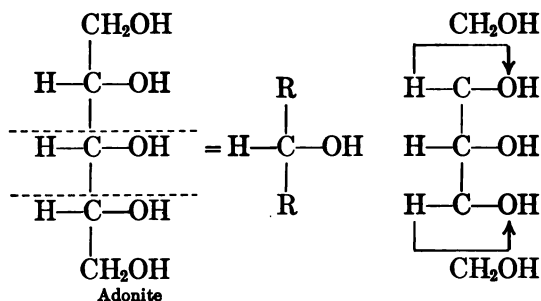
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From these are obtained on reducing the aldehyde groups to primary alcohol radicals, the following alcohols, the pentites.



Adonite and xylite are optically inactive although each contains two asymmetric carbon atoms. The central carbon atom in the pentose loses its asymmetry when the carbonyl group is changed to carbinol, for in the case of adonite the two groups marked off by the dotted lines are alike and there exists accordingly the same type of *internal compensation* with respect to influence on light, as was seen in mesotartaric acid (123).



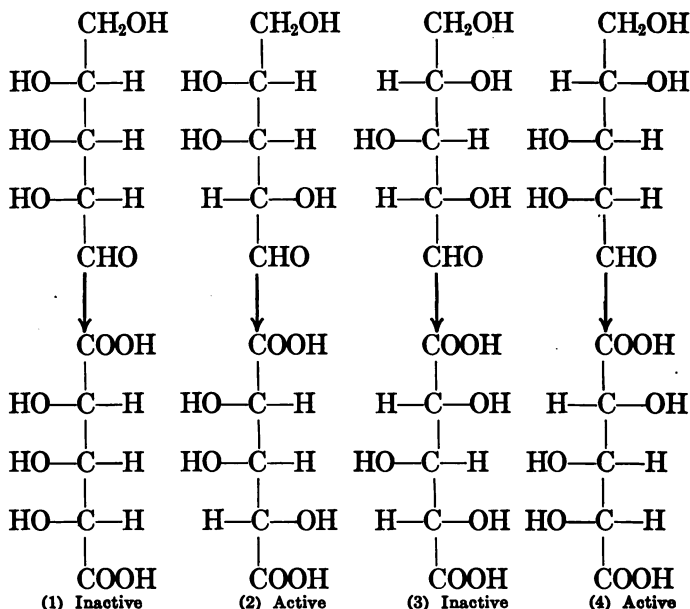
When the symmetry of the molecule is destroyed by oxidation of one primary alcohol radical, the central carbon atom again becomes asymmetric and optical activity is restored. A simple test as to whether a compound is inactive because of intramolecular compensation, is to determine whether by rotating the projection formula  $180^\circ$  in the plane of the paper it can be made to coincide with the projection formula of its mirror image. Whenever the two formulæ can be made to coincide, the molecules which they represent are identical and therefore cannot be optically different. l-arabinose and l-xylose and possible d-ribose occur in nature, while lyxose does not.

**152. Determination of Structure.** — We may now in-

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quire in what way it is possible to decide which of the several formulæ (1-8) of the aldopentoses is to be assigned to each of the naturally occurring sugars. If the projection formula for each one of the four pentoses having different configuration can be determined, the other four, being their mirror images, can at once be properly named.

If the four forms in question (page 296) be oxidized at both the aldehyde group and at the primary alcohol group there will result for each pentose form a trihydroxy glutaric acid of similar configuration.



Two of these will be active and two inactive because on converting both end carbon atoms into similar groups (car-

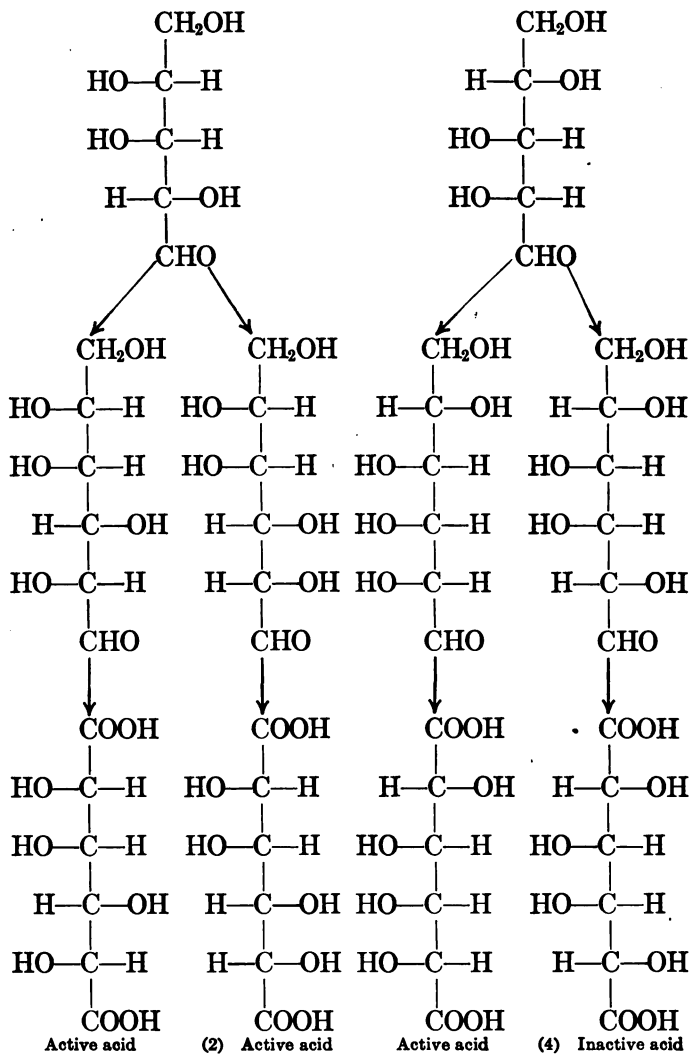
boxyl), the central carbon atom in (1) and (3) loses its asymmetry and the molecule presents internal optical compensation (151).

Arabinose and ribose yield the same osazone, so their difference in configuration must lie in the H and OH on the carbon atom next to the aldehyde group, since these only are displaced in osazone formation (p. 285). The pairs of formulæ which fulfill this condition are (1) and (2) or (3) and (4). Arabinose and ribose must be represented by one of these pairs.

Arabinose on oxidation yields an optically active trihydroxy glutaric acid, while ribose and xylose produce inactive acids. This necessitates assigning the formulæ (1) or (3) to ribose and xylose, and arabinose must be either (2) or (4). Lyxose must then be whichever of the formulæ (2) or (4) is not assigned to arabinose. But the fact that arabinose and ribose yield the same osazone shows that if arabinose is (2) ribose must be (1), or if arabinose is (4) ribose must be (3).

When a pentose is subjected to Kiliani's reaction (p. 290) the resulting hexose will present two different configurations, since when the hydroxyl group is formed in the cyanhydrin formation there is just as great a chance that it will take up its position on one side as another (see lactic acid, 66). When the hexoses derived from arabinose or xylose are oxidized to dibasic acids, both are found to be active, while those derived from lyxose are one active and the other inactive. The formulas for inactive acids must show internal compensation, since each contains two asymmetric carbon atoms.

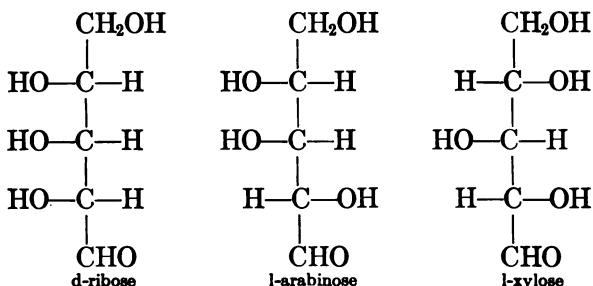
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It follows, therefore, that the formula of arabinose must be (2), and ribose which yields the same osazone must be (1), and lyxose, being the only pentose from which hexoses are derived yielding an active and an inactive dicarboxylic acid, must be (4). Xylose must then be represented by (3), the only one remaining.

## THE PENTOSES

**153.** The structural formulæ for the three biologically important pentoses are the following:



d-ribose has been found only in the nucleic acids. Judging from the amount of furfural obtained from various tissues when these are distilled with acids, the human body contains about 10.5 grams of pentose. l-arabinose and l-xylose are apparently not found in nature in the free state, but only in the form of their polysaccharides, araban and xylan (162) in the gums and woody tissues of plants. The pentoses are water-soluble and show the general properties of alcohols and aldehydes. l-arabinose is obtained from the hydrolysis of gum arabic, peach gum, cherry gum, etc. It crystallizes in prisms and has a sweet



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taste. It is dextrorotatory, its designation l-arabinose being due to its stereochemical relationship to glucose (155). It melts at 160°.

l-xylose is formed by hydrolysis of xylan, which is found to the extent of 17–25 % in the straw of wheat, rye, and other cereal grains. It crystallizes in doubly refractive prisms which melt at 144–145°.

In marked contrast to the more common hexoses, the pentoses are incapable of oxidation in the animal body except to a very slight extent. After the administration of even small doses by mouth they appear in the urine. In the case of certain individuals, there is excreted regularly in the urine, regardless of the character of the diet, a considerable amount of a pentose which has not been identified with certainty, but is probably arabinose or ribose. As much as 36 grams per day has been reported in the urines of such persons. This chronic *pentosuria* appears to be without ill effects, and is apparently hereditary.

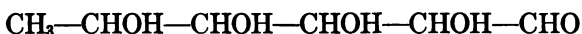
Temporary pentosuria frequently follows the ingestion of fruits and berries, many of which contain pentoses or soluble pentosans.

**Reactions of Pentoses.** — The reaction for the estimation of the pentoses or their polysaccharides depends upon the ready formation of furfural on treatment with mineral acids. The furfural produced is distilled off with steam and is precipitated with phloroglucinol (194). The latter is a cyclic trialcohol compound with which furfural forms a very insoluble compound on condensation. From the weight of furfural phloroglucide the pentose content of the sample is estimated. Barbituric acid (139) by virtue of its

hydroxyl group likewise condenses with furfural to form a very insoluble product, which has been made the basis of a quantitative estimation of the pentoses.

With certain other cyclic polyalcohols the pentoses in acid solution give characteristic color reactions. Most important is the colored derivative with *orcin* (196).

**154. Methyl Pentoses.** — There is found in nature a class of compounds called *glucosides* (161) which contain a hexose, a disaccharide, or a methyl pentose in union with some other substance. The second substances vary greatly in their chemical character, but in most instances they are alcohols. They are found in seeds, roots, leaves and bark of plants, and are broken up by acids or by specific enzymes, but not by alkalies, into their constituents. Among these glucosides quercitrin, xanthorhamnin and certain of the saponins (161) yield the methyl pentose *rhamnose*. This sugar is still occasionally referred to as isodulcite, a name which it once held owing to the mistaken belief that it was a hexahydric alcohol. Its formula is



**Rhamnose** is crystalline, the crystals containing one molecule of water. It melts at 93°.

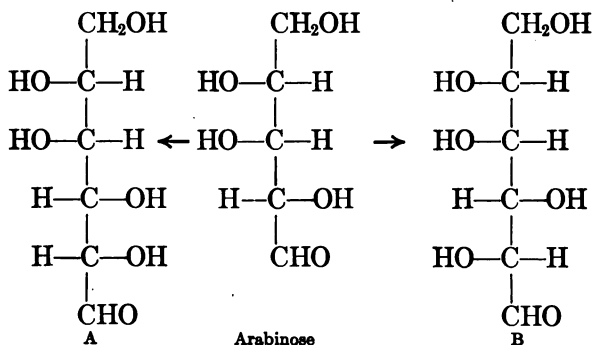
Other methyl pentoses found in nature are *fucose* in the form of the polysaccharide fucosan in certain seaweeds, and *chinovose* in the form of the glucoside chinovin found especially in cinchona bark.

**155. The Hexoses.** — There are sixteen possible stereochemical isomers of the sugars having the formula

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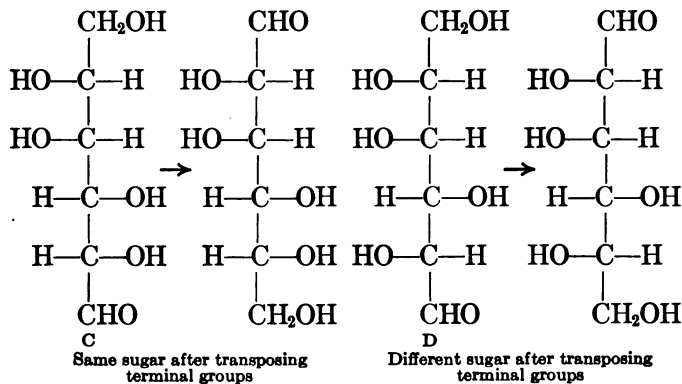
$\text{CH}_2\text{OH}-(\text{CHOH})_4-\text{CHO}$ . These represent eight forms and their mirror images. Of the eight pairs of sugars possible, two pairs are unknown, so that but six need be considered. Their structural formulæ are arrived at through their relation to the pentoses and the optical properties of the dibasic acids which they yield on oxidation.

When Kiliani's reaction (151) is applied to arabinose, there are obtained on reducing the resulting lactone two aldohexoses which are very common in nature, viz., glucose and mannose. It has been pointed out in describing the synthesis of hexoses from pentoses that the only difference possible must be due to the difference in position of the hydroxyl group on the carbon atom adjoining the aldehyde group. Glucose and mannose must be represented by the following two structures, A and B:—

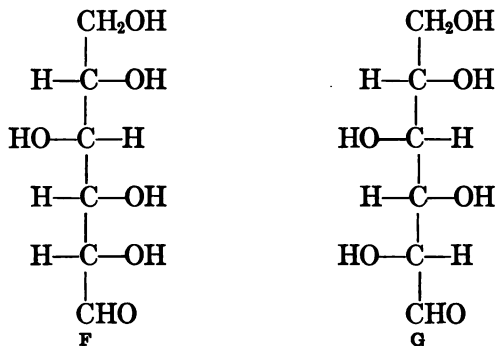


When glucose is oxidized, it yields a dibasic acid called *saccharic acid* (p. 313). One of the hexoses not found in nature, but obtained by Fischer by synthesis, viz. gulose, also yields on oxidation saccharic acid. This being the

case, the arrangement of the H and OH groups on all the four central carbon atoms must be alike in glucose and gulose, for these carbon atoms and their H and OH groups are not affected in any way by transforming the sugar into saccharic acid. It follows that the difference between glucose and gulose must be explainable as the result of the asymmetry due to the difference in position of the aldehyde and primary alcohol groups with respect to the peculiar arrangement of the rest of the molecule. It also follows that any formula which is the *same* when the CHO and CH<sub>2</sub>OH groups are transposed cannot represent glucose and gulose, for such a formula could not represent two different sugars. In the following formulæ C fulfills the last condition, while D, on transposing the end groups, leads to a different sugar.

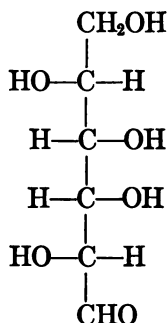


Glucose is therefore represented by the formula D and mannose is C. The formula F must accordingly represent gulose.



Idose, another sugar not found in nature but obtained synthetically, yields the same osazone as gulose, and their difference in structure rests therefore in the positions of the H and OH adjacent to the aldehyde group, since only these two are affected in osazone formation. This is further supported by the fact that xylose when subjected to Kiliani's reaction yields a mixture of gulose and idose. It has been already shown that gulose is represented by F, so idose must have the structure G.

d-galactose is a naturally occurring sugar. On reduction it yields an inactive hexahydric alcohol and on oxidation an inactive dibasic acid. When converted by Kiliani's reaction into two heptonic acids and on further oxidation of the latter into pentahydroxy pimelic acids, both products are optically active. From considerations analogous to those described in arriving at the structures of other hexoses, the formula ascribed to galactose is the following:



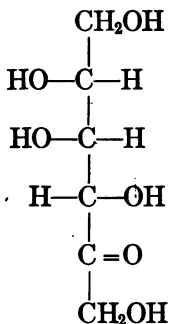
**156. The Ketoses.** — There are found in nature but two representatives of the ketohexoses, viz. fructose and sorbose. The latter is very rare, but the former is one of the very widespread and important sugars.

d-fructose is found together with glucose in sweet fruits and is chemically combined with it in cane sugar, with glucose and galactose in raffinose, a trisaccharide found in cotton seed, with mannose as mannotetrose found in manna, and with galactose in lupeose, a tetrose found in the seeds of the lupine. There is a starch-like polysaccharide, inulin, in the tubers of the dahlia, which yields fructose on hydrolysis.

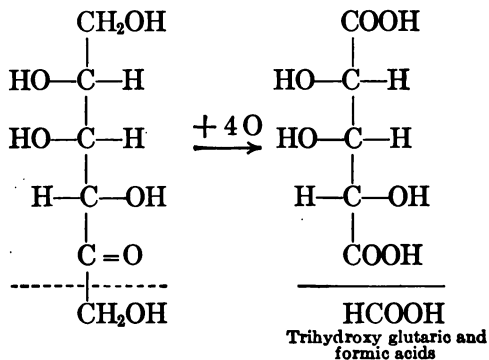
d-fructose is found in nature. It is levorotatory, notwithstanding its designation as d-fructose. Fischer designated as the d-, l-, or i- form all monoses which are derived from a d-, l-, or i-hexose respectively. d-fructose can be derived from d-glucose, hence its name. The letter denoting the form of a monose signifies to what optical form of hexose the monose is related, and not the direction of its rotation of the plane of polarized light.

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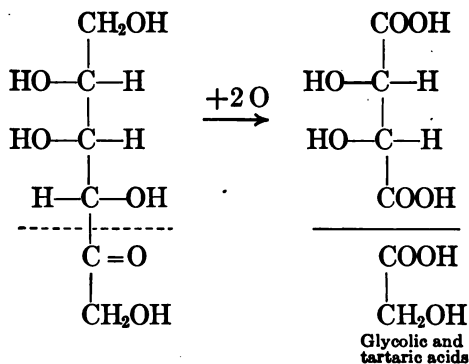
It is distinctly sweeter than any other sugar, and is more unstable than the aldohexoses. The constitution assigned to it is :



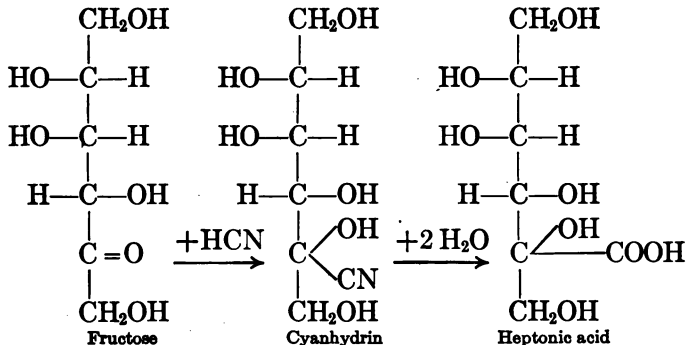
On oxidation it yields formic, glycolic, tartaric, and trihydroxy glutaric acids.



Since the cleavage may take place on one side of the carbonyl group as well as on the other, this group of oxidation products shows that the carbonyl group is but one removed from the terminal carbon atom.



Whereas the aldopentoses and aldohexoses yield normal carbon chain derivatives when subjected to the cyanhydrin synthesis (page 287), fructose yields an acid with the following structure :

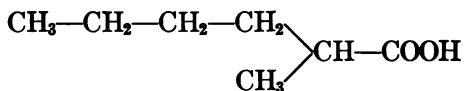


This harmonizes with the assumption that the structure assigned to fructose is correct, for the ketone structure of fructose must necessarily lead to the formation of a branched carbon chain.



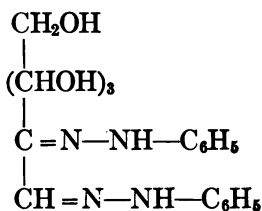
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This heptonic acid when reduced by heating with hydriodic acid (149) is changed into methyl-*n*-butyl acetic acid



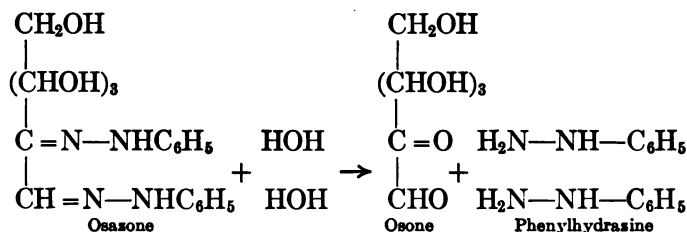
which has been synthesized by the Claisen reaction (127).

The same osazone is obtained from d-fructose as from d-glucose. It is therefore evident that the configuration of the molecules of these hexoses differ only in the ketone group and its adjacent terminal carbon atom. The identity of the osazones serves to confirm the idea that in glucose the  $\alpha$ -carbon atom and in fructose the terminal carbon atom react with a second molecule of phenylhydrazine after hydrazone formation has taken place. In other words, it is definite evidence that in the osazones the two phenylhydrazine groups are united to adjacent carbon atoms. The osazone from these two sugars, which may properly be called glucosazone or fructosazone, has the following constitution :



Glucose may be converted into fructose by warming the osazone with hydrochloric acid. The two phenylhydrazine groups are separated by hydrolysis and there results

an *osone*, a compound containing an aldehyde and a ketone group :



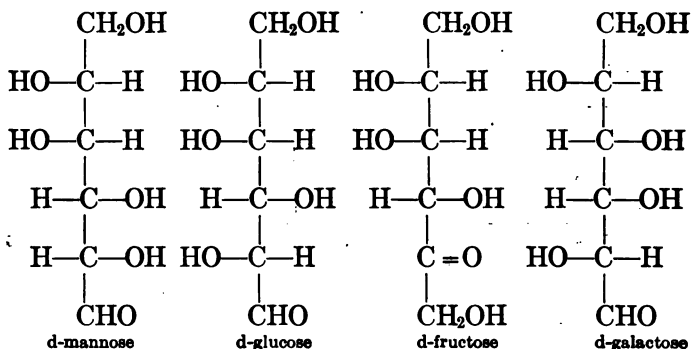
On careful reduction the aldehyde group is reduced to a primary alcohol and fructose is formed. This reaction is general for the conversion of aldoses into ketoses.

In harmony with what has been said regarding which two carbon atoms react in the formation of the osazones, it is found that while d-glucose and d-mannose yield different hydrazones they yield the same osazone. It has been shown already that the molecules of these sugars differ only in the positions occupied by the H and OH linked to the  $\alpha$ -carbon atom (152).

Heptoses, octoses, and nonoses, aldoses containing seven, eight, and nine carbon atoms, have been prepared by Fischer from the hexoses by the cyanhydrin synthesis. These compounds are not found in nature. It is of biological interest that they are not fermentable by yeast.

**157. Special Properties of the Hexoses.** — Among the many possible aldo- and keto-hexoses, there are only four which are of great importance as natural products :

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**Mannose** is seldom found in nature as such and only in small amounts. It forms in plants a cellulose-like substance, mannocellulose (mannan), in the cell walls, and in this form occurs in large quantities, an especially good source being the ivory nut. Mannose is obtained as a hard, solid amorphous mass which is deliquescent and dissolves easily in water, slightly in alcohol and is insoluble in ether. It is identified as the phenylhydrazone which melts at 195–200°.

On reduction with nascent hydrogen mannose is converted into the hexahydric alcohol, *mannite*. The latter is found in considerable amounts in manna, that from the ash containing 30–60 %. Mannose is easily fermentable by yeast. It is crystalline and melts at 132°.

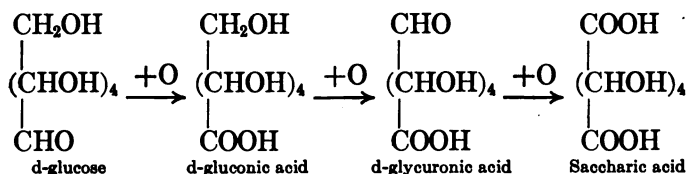
**d-glucose** (dextrose, grape sugar) is found widely distributed with fructose in ripe fruits and other parts of plants, including the nectar of flowers. It is formed from the hydrolysis of cane sugar, malt sugar, and milk sugar, starch, etc. It is the sugar which is a normal constituent of the blood and lymph, being present to 1 part

in 1000. In diabetes, a disease of the pancreas, it occurs in the urine sometimes in large amounts.

On reduction of glucose the hexahydric alcohol d-sorbitol is formed, and on oxidation gluconic acid, analogous to mannonic acid, and on further oxidation the dibasic saccharic acid, analogous to manno-saccharic acid.

d-glucose crystallizes from alcohol in water-free form, and from water as a hydrate,  $C_6H_{12}O_6 + H_2O$ . Water-free glucose melts at  $146^\circ$  and at  $170^\circ$  loses water from its H and OH groups, several molecules of glucose condensing to a polysaccharide *glucosan*. By treating glucose with dehydrating agents, such as strong acids, several molecules are condensed to form polysaccharides, complexes having a high molecular weight.

On oxidation of d-glucose the aldehyde group is first attacked and is converted into *gluconic acid*, and on further oxidation the primary alcohol group is converted successively into an aldehyde and then into a carboxyl group:



Although this is the course of the oxidation of glucose in the laboratory, and although animals regularly oxidize large amounts of glucose, these acids do not represent the course of the first steps in the destruction of sugar by the living organism. Instead the glucose molecule is dissociated into simpler compounds containing but three and

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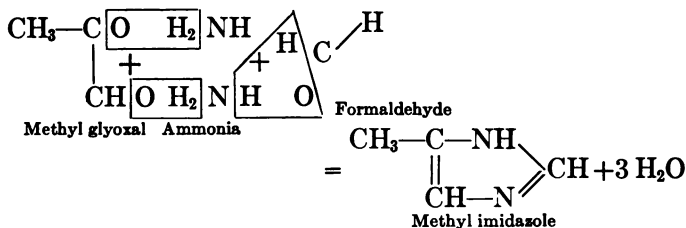
two carbon atoms, and it is these which are oxidized. The first step in the biological degradation of the sugars is therefore not oxidative but hydrolytic (164).

d-glucose is the most easily utilized of the hexoses. In healthy persons the capacity to utilize this sugar is as great as the capacity of the digestive tract to absorb it. Healthy young men have been known to absorb more than a pound of glucose within twenty-four hours without the appearance of sugar in the urine. It is likewise easily fermented by yeasts, in which process it is converted into alcohol and carbon dioxide (see fermentation).

### ACTION OF ALKALIES ON GLUCOSE

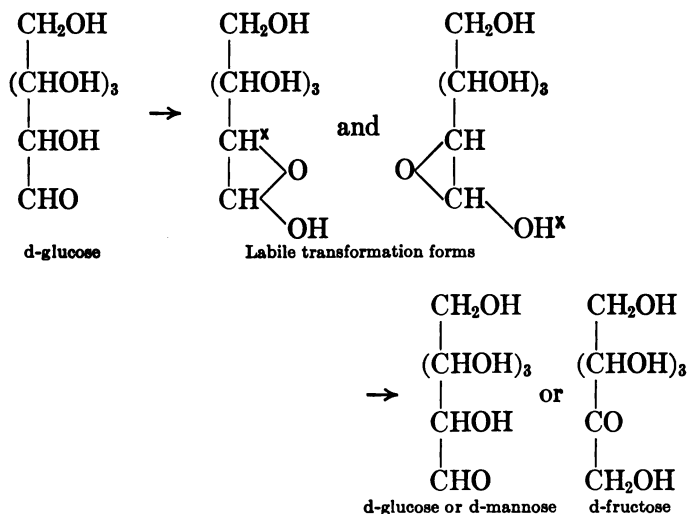
When allowed to stand for several months with dilute alkali glucose is converted to the extent of 50–60% into inactive lactic acid, .5–2% into formic acid, and 30–50% into several hydroxy acids. Among other cleavage products formed by alkalies is *methyl glyoxal*, the aldehyde of pyruvic acid.

A reaction of biological interest is the formation of *methyl imidazole* by the action of ammonia and zinc hydroxide on glucose. This illustrates in a suggestive way the possibility of the formation of certain cyclic compounds within the animal body through the participation of carbohydrate. It will be recalled that one of the amino acids, histidine (138), derived from proteins, contains the imidazole ring. The formation of methyl imidazole from glucose and ammonia is best explained as the result of the interaction of ammonia with the dissociation products of glucose, methyl glyoxal, and formaldehyde:



In solution in water containing the slightest trace of alkali (OH ions), glucose is in part transformed into d-fructose and d-mannose. The explanation of this change, first studied by de Bruyn and van Eckenstein is as follows:

The aldose d-glucose, in water solution passes to some extent into the forms illustrated by the following structural formulæ:



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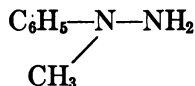
The change is believed to take place through the lability of one hydrogen atom marked X in the intermediate forms whereby it can wander from one to the other of the two neighboring carbon atoms. By the shifting of a hydrogen from the end carbon atom to the second an aldose would be regenerated, but by the law of chance the hydroxyl group would take its place on one side of the chain as frequently as the other, and d-glucose would be regenerated or d-mannose would be formed accordingly. By a shifting of the hydrogen atom from the second to the end carbon atom a ketone sugar d-fructose would result. When therefore any one of the three sugars d-glucose, d-mannose, or d-fructose is in solution in the presence of a low concentration of hydroxyl ions, it will pass in part into the other two, until a certain proportion exists among the three kinds of molecules, *i.e.* each form is in dynamic equilibrium with the other two. If by some means the glucose is removed from the system, more will be formed.

This observation is of the greatest importance in that it enables us to understand how an animal may absorb from the digestive tract mannose or fructose and yet these never be present in the blood. They are always transformed into d-glucose if the absorption is not too rapid, in which case the fructose and mannose are said to exceed the assimilation limit since they escape into the urine.

d-glucose yields a phenylhydrazone which melts at 144–146°, and an osazone which melts at 206°. On reduction it yields the hexahydroxy alcohol d-sorbitol.

**d-fructose** is actually levorotatory, but is called the dextro form because of its structural relationship to d-

glucose. Although d-fructose yields the same osazone as do d-glucose and d-mannose, it is easily distinguishable from these by its peculiar behavior with *methyl phenylhydrazine*:



With this methyl-substituted phenylhydrazine d-fructose and other ketoses yield osazones. The aldoses, on the other hand, do not react with this reagent beyond the hydrazone stage under ordinary conditions. The methyl phenylosazone of fructose melts at 158–160°.

The capacity of the animal organism to utilize fructose is much less than for d-glucose. d-fructose is easily fermentable by yeast.

An extremely interesting observation is the formation of d-fructose from *d-mannite* by a kind of fermentation induced by *Bacterium xylinum* Brown, through which the alcohol is oxidized to a ketone.

**d-galactose** is present in milk sugar in union with d-glucose. It also occurs in certain polysaccharides, as agar-agar, and in certain glucosides. It exists in the brain in considerable amount in union with a fatty acid and a base of unknown chemical nature. The hexose itself has never been found in the free state in either plants or animals. Galactose is easily distinguishable from the other hexoses by the insolubility in dilute nitric acid of the dicarboxy acid, *mucic acid*, which results on oxidation of the sugar with nitric acid. Mucic acid is so insoluble and is formed so nearly quantitatively that its formation



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serves as the best available method of estimating galactose or galactose-yielding polysaccharides.

d-galactose is much less readily utilized in the animal body than is either glucose or fructose, and on the ingestion of even moderate amounts is eliminated in part unchanged in the urine.

**158. The Disaccharides.** — There are three sugars of great biological interest which yield on hydrolysis two molecules of hexose. The molecular weights of all of them correspond to the formula  $C_{12}H_{22}O_{11}$ . They are *sucrose*, or cane sugar, which yields on hydrolysis one molecule of d-glucose and one of d-fructose; *maltose*, or malt sugar, which yields two molecules of d-glucose; and *lactose*, or milk sugar, which yields one molecule of d-galactose and one of d-glucose.

**Sucrose**,  $C_{12}H_{22}O_{11}$ , occurs in the juices of many plants, especially sugar cane and sugar beet. As much as 16–20 % of the dry substance of the plant is sucrose. It crystallizes readily. The sugar is extracted from the finely rasped beets with warm water and the solution treated with lime, which causes the neutralization of acids in the juice, and is then boiled to coagulate the proteins. The solution is then treated with carbon dioxide to precipitate most of the calcium, and after this with sulphur dioxide whose reducing action discharges the color. It is again boiled and filtered, and the filtrate evaporated under diminished pressure to crystallization. The mother liquor from the crystals is molasses. The molasses yields another portion of sucrose on treatment with lime or strontium hydroxide, an insoluble calcium or strontium *saccharate* being formed. The

latter is decomposed by carbon dioxide and the liquid, freed from solid calcium or strontium carbonate, yields a crop of crystals of sugar. The molasses, which contains much glucose, is in great part fermented for the preparation of rum or alcohol for industrial purposes.

Sucrose forms large monoclinic crystals which are easily soluble in water and melt at  $160^{\circ}$ , then solidify to a glassy mass and on further heating become brown with the formation of caramel. The specific rotation of cane sugar is, for a solution of about 25 % strength :

$$[\alpha]_D = +66.5^{\circ}$$

The rotatory power is made use of in the estimation of sucrose. On boiling with dilute acids, it is converted into d-glucose and d-fructose. The resulting solution rotates the plane of polarized light to the left, since the levorotatory power of fructose is  $[\alpha]_D = -93^{\circ}$  while for d-glucose or dextrose  $[\alpha]_D = +52.7^{\circ}$ . Since the direction of rotation changes when cane sugar is hydrolyzed, the process is called inversion, and the product *invert sugar*.

The same conversion of sucrose into glucose and fructose is brought about by an enzyme *invertase*, which is present in yeast and in the mucous membrane of the small intestine. The rate of inversion of cane sugar by acids has been very carefully studied, and it has been found that it is proportional to the concentration of the hydrogen ions present. The hydrogen ion is therefore the catalytic agent for this hydrolytic reaction.

Sucrose does not reduce the oxides of the heavy metals

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(*e.g.* Fehling's solution) as do glucose, fructose, mannose, and the other aldoses and ketoses, nor does it form compounds with hydrazines. It does not therefore contain a carbonyl (aldehyde or ketone) group, but on hydrolysis to glucose and fructose an aldehyde and a ketone group are formed. It contains, however, eight hydroxyl groups, since it yields an octa-acetyl derivative.

Sucrose is regarded as a glucoside of d-fructose (161). It cannot be utilized directly by an animal, being excreted in the urine when introduced directly into the blood. In the digestive tract it is hydrolyzed into glucose and fructose before absorption.

**Maltose**,  $C_{12}H_{22}O_{11} + H_2O$ , is found in small amounts in many plants. It is the end product of the action on starch of the enzyme *amylase* of the saliva of the omnivorous animals, including man. It has been found in human urine in disease of the pancreas, but in the normal organism maltose is readily utilized either when introduced into the alimentary tract or directly into the blood. The blood contains an enzyme *maltase* which converts maltose into two molecules of d-glucose. This change is likewise effected by heating with dilute acids. There is no corresponding enzyme in the blood or tissues for the hydrolysis of sucrose or lactose.

Maltose reduces solutions of the oxides of the heavy metals, which indicates that it contains a carbonyl group. Maltosazone melts at  $205^{\circ}$ .

Isomaltose is a disaccharide which is formed by the dehydrating action of strong hydrochloric acid on a concentrated solution of glucose. Its osazone melts at  $200^{\circ}$

and is more soluble in water than is maltosazone. Its stereochemical configuration is sufficiently different from maltose to make it non-fermentable with yeast. The enzymes of yeast do not hydrolyze it to hexoses, but the enzyme *emulsin* found in the almond converts it into two molecules of glucose.

**Lactose or Milk Sugar**,  $C_{12}H_{22}O_{11} + H_2O$ , is found nowhere but in the milk of animals. It contains a carbonyl group, since it reduces certain oxides of the heavy metals. Its osazone melts at  $200^\circ$ .

In the animal organism lactose behaves as does cane sugar. When taken into the alimentary tract, it is hydrolyzed by the enzyme *lactase* into d-glucose and d-galactose before being absorbed; and if introduced directly into the blood, is principally excreted unchanged in the urine. The lactose of the milk is derived from d-glucose and not from the food.

Melibiose is isomeric with lactose and yields the same hexoses on hydrolysis. It results together with d-fructose from the action of dilute acids or of *invertase* upon the trisaccharide raffinose. Like lactose, it is a reducing sugar. It resembles lactose in being hydrolyzed by *emulsin*, but differs from it in not being cleaved by *lactase*.

**159. The Stereochemical Configuration of the Sugars Determines their Biological Value.** — Of the sixteen isomers of the aldohexoses only three are readily utilized by the higher animals, and of these three, d-glucose, d-fructose, and d-mannose, only the former has a high assimilation limit. Galactose is utilized with more difficulty than the three first named.

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A similar relationship holds in the case of the disaccharides. Before these can be utilized biologically they must be converted into the  $C_6$  sugars, and there is a marked difference in the extent to which various organisms are prepared with the specific enzymes necessary for their cleavage. Thus the invertase of yeast, but not the maltase and lactase, act on cane sugar. Invertase and lactase do not cleave maltose. Emulsin does not hydrolyze any of these disaccharides. Certain of the molds are provided with all of these enzymes.

The limitations of the digestive tract are similar to those of yeasts. The mucous membrane of the intestine in all animals contains invertase and maltase and usually lactase. The blood contains maltase, but no invertase or lactase.

Yeasts show among the races great variation in their capacity to effect the hydrolysis of the disaccharides. Thus, the yeast which induces alcoholic fermentation of milk, forming *kephir*, contains lactase, while beer yeast does not. The latter, however, can cleave cane sugar and ferment the resulting sugars. Many yeasts contain both invertase and maltase, and can ferment both these sugars, but *Saccharomyces Marxianus* contains only invertase and can ferment therefore sucrose, but not maltose. *Saccharomyces octosporus*, on the other hand, can ferment maltose but not sucrose, and *Saccharomyces apiculatus*, which is capable of fermenting d-glucose, d-mannose, and d-fructose, contains no enzyme for the hydrolysis of any of the disaccharides, and cannot ferment the latter.

160. **Raffinose**,  $C_{18}H_{32}O_{16} - 5 H_2O$ , is a trisaccharide found in small amount in the sugar beet and therefore in considerable amount in molasses. It is especially plentiful in the cotton seed (10 %) and is a constituent of *Eucalyptus manna*. On hydrolysis with dilute acids it is first converted into fructose and melibiose, and the latter into d-glucose and d-galactose. Top yeast effects the cleavage of raffinose into d-fructose and melibiose, and bottom yeasts ferment it completely. Emulsin converts raffinose into galactose and cane sugar.

### THE GLUCOSIDES

161. In a manner analogous with the reaction of the aldehydes with alcohols to form acetals (32), the aldoses can react with alcohols to form the glucosides. Many such compounds occur in nature in plants, these usually containing an aromatic alcohol, aldehyde, or acid, but also other classes of compounds. The carbohydrate group is in most cases glucose, but glucosides are also known which yield galactose, rhamnose, and disaccharides. The leaves of *Indigofera tinctoria* and of *Isatis tinctoria* contain a glucoside *indican*, from which the dye indigo results by a process of fermentation. The madder root contains among other glucosides *ruberythric acid*, which yields the red dye *alizerin*. The leaves of *Digitalis purpurea* yield the glucoside *digitalin*, which exerts a peculiar action on cardiac muscle. Willow bark contains salicin, from which salicylic acid (209) is derived. The roots of fruit trees, as apple, peach, etc., yield the glucoside *phlorizin*, which is much employed in inducing an experimental glycosuria in animals

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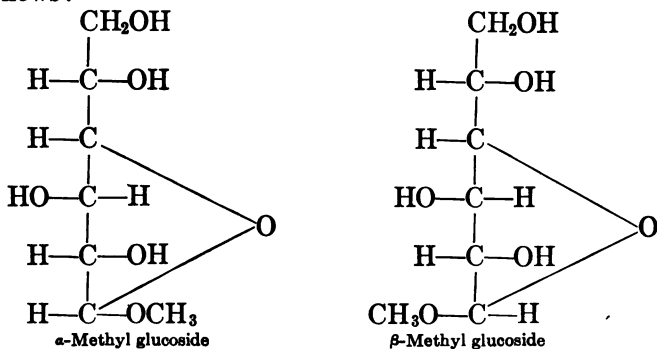
for biochemical studies. The roots of *Spiræa* contain *gaultherin*, mustard seeds yield *myrosin*, etc.

One of the best known of the glucosides is *amygdalin*, from the bitter almond. Solutions of amygdalin do not reduce solutions of the heavy metals, a fact which is taken to indicate that there is no free aldehyde group. After hydrolysis with dilute acids the presence of glucose can be detected by the reduction of Fehling's solution, and by the formation of an insoluble osazone (p. 286) which melts at 205°. Benzaldehyde can be detected by its odor, and HCN by its precipitate with silver nitrate. It is soluble in alcohol and can be crystallized from this solvent. Emulsin, an enzyme contained in the almond, hydrolyses amygdalin into benzaldehyde (204), hydrocyanic acid, and two glucose molecules. Water extract of beer yeast contains an enzyme which splits off hydrolytically but one molecule of glucose and leaves the combination benzaldehyde, hydrocyanic acid, and glucose, the glucoside of mandelic acid nitrile (206).

### CONSTITUTION OF THE GLUCOSIDES

The best-known synthetical glucosides are those from glucose and methyl alcohol. When a concentrated solution of d-glucose in methyl alcohol is treated with gaseous hydrochloric acid, there result two compounds known as  $\alpha$ -methyl glucoside and  $\beta$ -methyl glucoside. The  $\alpha$ -form is dextrorotatory and is soluble in 200 parts of alcohol; while the  $\beta$ -form is levorotatory and is soluble in 66.7 parts of alcohol at 100°. They can therefore be separated by their different solubilities. Maltase hydrolyzes the

$\alpha$ -glucoside but not the  $\beta$ -form, while emulsin hydrolyzes the  $\beta$ -form but not the  $\alpha$ -form. The natural glucosides are in general hydrolyzed only by emulsin, and for this reason they are termed  $\beta$ -glucosides. The structural formulæ assigned to  $\alpha$ - and  $\beta$ -methyl glucosides are as follows:

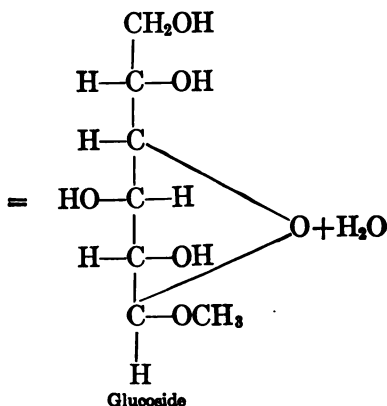
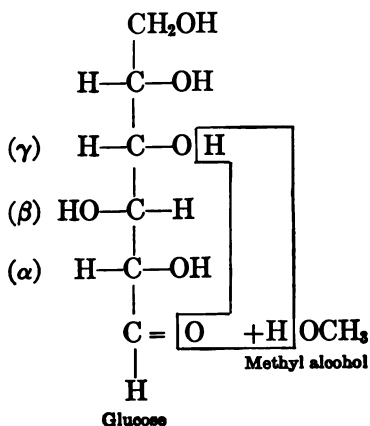


The reasons for assigning these constitutional formulæ are the following:

1. Only a single molecule of alcohol reacts with one of glucose, with the elimination of a molecule of water. One of the secondary alcohol radicals must therefore enter into the reaction. This is in all probability the  $\gamma$ -hydroxyl group, since this is the one which reacts in the formation of lactones (125), and since no compounds other than those containing  $\gamma$ -hydroxyl groups form glucosides. The ease with which the glucosides are decomposed by hydrolysis argues strongly against the union of the alcohol radical directly to carbon, and for the assumption of linkage through oxygen as in the ethers. The mechanism of glucoside formation may therefore be represented thus:



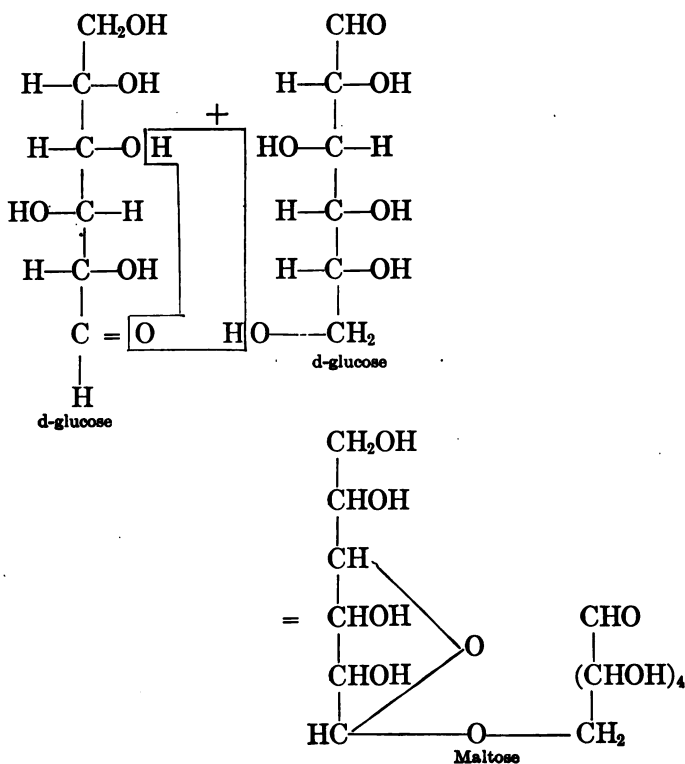
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**Mutarotation.** — Freshly prepared solutions of glucose rotate the plane of polarized light nearly twice as much as they do after standing for a time. If the water is evaporated and the sugar crystallized it will, on again dissolving it, show the high rotation value. There must

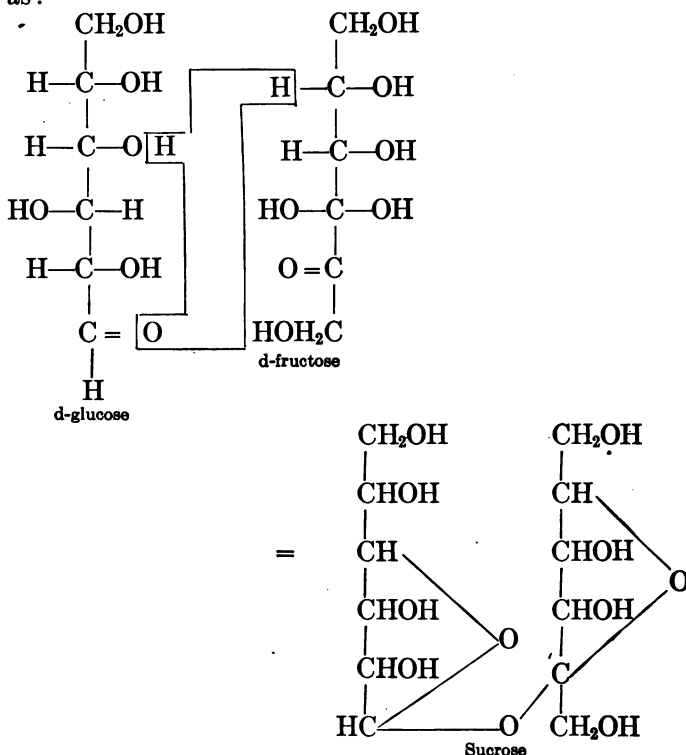
occur a reversible change during evaporation. It is believed that the change in rotatory power is the result of the interaction of a molecule of water with one of glucose, analogous to methyl alcohol and glucose, with the loss of a molecule of water and the formation of a structure analogous to a glucoside, but with OH in place of the OCH<sub>3</sub>.

Maltose is regarded as a glucoside of glucose:



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Sucrose, which contains no carbonyl group, is represented as :



Emil Fischer has suggested the comparison of the specific action of enzymic action in the hydrolysis of sugars and other compounds, with the relationship between lock and key. The stereochemical structures of both the enzyme and the molecules of the substrate determine whether they can interact. This specificity of ferment

action is of the greatest significance for the life of the animal or plant cell.

The union of galactose in the galactolipins of the brain and of ribose in nucleic acids is probably of the nature of glucosides.

#### THE POLYSACCHARIDES

**162. Starch** ( $C_6H_{10}O_5$ )<sub>n</sub> (*amylum*) is a non-crystalline carbohydrate produced by plants as a reserve material. It is closely related to cellulose on the one hand, a compound whose peculiar properties fit it to be the skeletal tissue of plants, and to the simple hexoses and disaccharides on the other, into which it is readily converted by hydrolysis. Starch is insoluble in water and exists in grains, tubers, fruits, etc., in the form of grains. These consist of at least two kinds of carbohydrates: *granulose*, which is colored blue by iodine, and starch cellulose, which is not. The blue color produced by iodine is discharged on heating but reappears on cooling. Starch has a very high molecular weight (32,000) and when boiled with water undergoes incipient hydrolysis and is changed into *soluble starch*. The latter forms an opalescent colloidal solution.

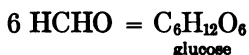
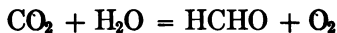
The amylase of the saliva of certain animals rapidly causes hydrolysis of starch into a series of simpler carbohydrates, the dextrines, the final product being maltose. Acid hydrolysis converts starch into d-glucose.

The form and appearance of the starch grains vary with their origin. It is a simple matter for one familiar with the forms to identify by microscopical methods the source of the starch.

Starch is not the first product of the synthetic activity

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of the plant. The latter absorbs carbon dioxide from the air and water and inorganic salts, including nitrates, from the soil. It is generally assumed, since formaldehyde is present in minute amounts in functioning leaves, and the latter, as pointed out earlier (151), is polymerized to a mixture of hexoses, that it is the first product formed :



The formation of starch is not dependent on the formation of glucose. Leaves which have been kept in the dark until they are starch-free and then in the dark are floated on sugar solutions quickly form starch. d-glucose and d-fructose are most readily utilized for this purpose, but certain plants can use mannose and even galactose for starch synthesis. Stereochemical transformation is, of course, necessary in these cases.

Starch is easily hydrolyzed by acids, but only with great difficulty by alkalies.

**Dextrines** correspond to the same empirical formula as starch, but their molecular weight is much smaller. It is assumed that there are a large number of dextrines of different molecular complexities, but only two can be readily distinguished. *Erythrodextrine*, which gives a red color with iodine, is first formed by the action of amylase on starch; and *achroodextrine*, which gives no color with iodine, is formed somewhat later.

**Cellulose** is much more resistant than is starch. It is not acted upon by enzymes formed by the higher animals

or plants, and is not easily decomposed by acids or alkalis. On treatment with strong acids under appropriate conditions the only product of its hydrolysis is d-glucose. Cellulose is found nearly pure in the cotton fiber, in linen, and in hemp, and is the principal constituent of wood. The latter, however, contains about half its dry weight of incrusting substances, known as lignin, pectins, and gummy substances.

There occurs in the covering of the tunicata, a group of animals, a polysaccharide *tunicin* which appears to be identical with cellulose. This is the only instance of the occurrence of cellulose in the animal kingdom.

When acted upon by concentrated nitric acid or by a mixture of nitric and sulphuric acids, cellulose is nitrated. According to the conditions, from one to six nitro groups are introduced in ester linkage for each of the  $C_6H_{12}O_5$  complexes in the molecule. A mixture of tri- and tetra-nitrates dissolved in a mixture of alcohol and ether constitutes *collodion*.

*Guncotton*, or pyroxylin, is the hexanitate of cellulose. When dissolved in acetone or ethyl acetate and the solution evaporated, the residue in granular form constitutes smokeless powder. A mixture of cellulose hexanitate with nitroglycerine and other substances forms ballistite, cordite, blasting gelatin, etc.

Cellulose forms several acetates when treated with glacial acetic acid and acetic anhydride in the presence of strong sulphuric acid. These are insoluble in water, but soluble in various organic solvents. Artificial gutta-percha is produced by evaporating a solution of tetra-

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acetyl cellulose in acetone. When a solution of cellulose acetate in glacial acetic acid is poured into alcohol, a precipitate is formed which contains much alcohol and burns without melting or leaving an ash and is sold as "solid alcohol."

Cellulose is indigestible in the alimentary tract of animals, but certain bacteria present there ferment it with the formation of carbon dioxide, methane, hydrogen, and formic, acetic, butyric, valerianic, and other acids. Certain molds and saprophytic plants secrete an enzyme, *cytase*, which dissolves cellulose. The products formed are not known.

Cellulose is insoluble in all ordinary solvents, but dissolves in an ammoniacal solution of copper oxide (Schweitzer's reagent), and in a solution of zinc chloride in hydrochloric acid.

**Hemicelluloses** are important constituents of nut shells and stony seeds of fruits, coconut rind, etc., and are present in considerable amounts in the seeds of legumes (pea, bean, etc.). On hydrolysis with acids they yield mannose, and those of the legumes especially galactose. A certain amount of arabinose and xylose is also usually formed. They are not well-characterized compounds therefore, and appear to be either mixtures of mannans, xylan, araban, galactan, or complex carbohydrates composed of complexes representing several kinds of sugars.

**Pentosans** are polysaccharides which correspond to the celluloses, but they yield on hydrolysis a pentose sugar. Thus *xylan*, which is present in the straws to the extent of 18-28 %, yields xylose; and *araban*, which occurs in cherry,

peach, and other gums and is the principal constituent of gum arabic, yields arabinose on hydrolysis. They are soluble in alkalies and are precipitated by alkaline copper solutions, as copper xylan, etc. Like the pentoses, they yield furfural on distillation.

**Pectins** are the constituents of fruit juices which cause the setting of jellies. Carrots, beets, and rhubarb are especially rich in these constituents. Their chemistry is not well understood. Preparations of pectins made by precipitation with alcohol yield both pentoses and hexoses, and in addition acids which seem to be of the type of gluconic acid.

**Plant Mucilages** are substances which swell in water and form mucilaginous solutions. As examples may be cited flaxseed mucilage, and those of the roots of salep and althea. They yield both pentoses and hexoses on hydrolysis, but their chemistry has not been thoroughly studied.

**Gums** contain the salts of as yet unidentified organic acids, and yield these acids and certain reducing sugars on hydrolysis. Arabinose, xylose, fucose, and galactose have been identified.

**Glycogen** is a polysaccharide contained in animal and in certain plant tissues which resembles soluble starch in certain respects, but gives a reddish color with iodine. It is soluble in cold water, forming an opalescent solution. It is formed by the condensation of a number of molecules of glucose, water being separated in the union of each two molecules. It is acted upon by *amylase*, which converts it into maltose as in the case of starch.

The glycogen content is higher in the liver than any



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other tissue, usually from 1 to 4 %, but the livers of highly fed animals have shown contents as high as 15 %. It is found in other tissues, especially muscles.

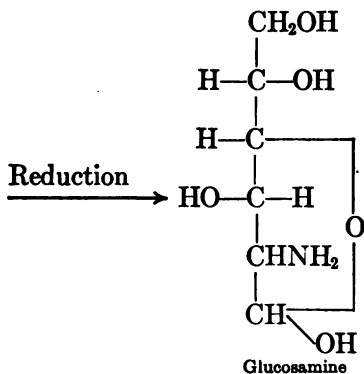
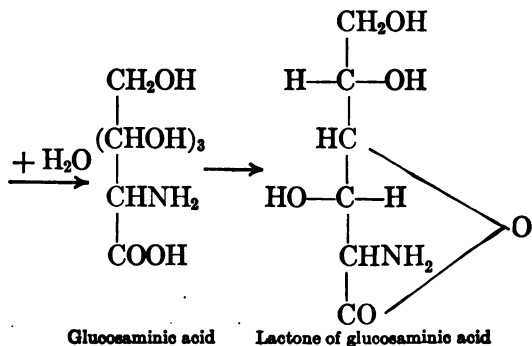
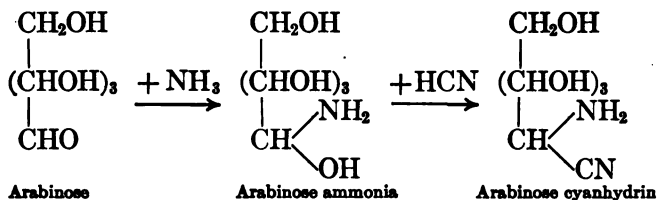
Among plants yeast is richest in glycogen. When animals or yeasts are starved the glycogen content decreases markedly, being slowly converted into glucose which passes into the blood to keep up the normal content of one part to one thousand of the latter. Glycogen is formed in the animal body from certain sugars other than glucose, as mannose, levulose, etc., but only as these are converted into glucose (157).

**163. Chitin** is a peculiar polysaccharide which forms the matrix of the shells of the crustacea (lobsters, etc.), the external covering and the lining of parts of the alimentary canal of insects, and the covering of certain worms (Hirudinea). When freed from incrusting calcium salts in the case of lobster shells chitin forms a leathery substance which on hydrolysis with mineral acids yields an amino derivative of glucose, glucosamine, the only nitrogen-containing carbohydrate.

On heating chitin with strong alkali, a treatment which does not change cellulose or tunicin, it is decomposed by hydrolysis into acetic acid and *chitosan*, which is soluble in acetic acid but is precipitated by alkalies. Chitosan is a base and forms salts with acids. On boiling it with acids it is hydrolyzed to glucosamine and a further amount of acetic acid.

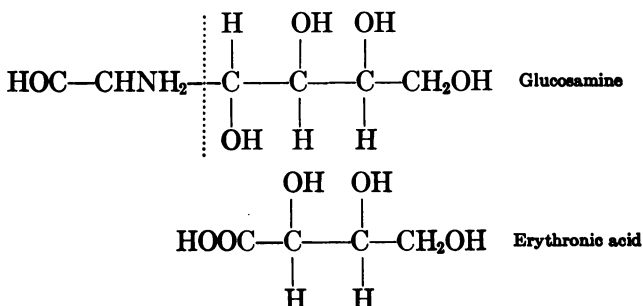
**Glucosamine**,  $C_6H_{11}O_5NH_2$ , is an amino sugar derived from many proteins on hydrolysis. It contains an aldehyde group, as is shown by its formation of an oxime with

hydroxylamine, and a hydrazone. Its constitution has been approximately established by E. Fischer, who synthesized it by the following procedure :

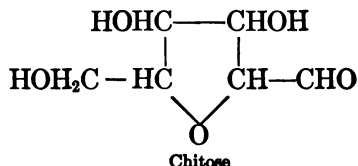


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It is not certain whether the amino group is on one or the other side of the carbon chain, and the compound may be either glucosamine or mannosamine. That the amino group is united to the carbon atom neighboring the aldehyde is made highly probably by the decomposition described by Neuberg, of glucosamine into erythronic acid (150) by boiling with barium hydroxide.



On treatment of glucosamine with nitrous acid the amino group is replaced by hydroxyl. The resulting hexose is however not glucose or mannose. It is known as *chitose*. It does not ferment, and does not yield a difficultly soluble osazone. By comparison with the synthetically prepared compound, Fischer assigned to chitose the following cyclic structure :



**Inulin** ( $\text{C}_6\text{H}_{10}\text{O}_5$ )<sub>n</sub> is a polysaccharide entirely analogous to starch, which is found as a reserve carbohydrate in

dahlia roots and other tubers of the Compositæ. On hydrolysis it yields only d-fructose. In the plant tissues where inulin occurs there is formed an enzyme, *inulase*, which effects its hydrolysis whenever growth begins. There is no inulase in the digestive secretions of animals and therefore no provision for the utilization of this carbohydrate.

## CHAPTER XVI

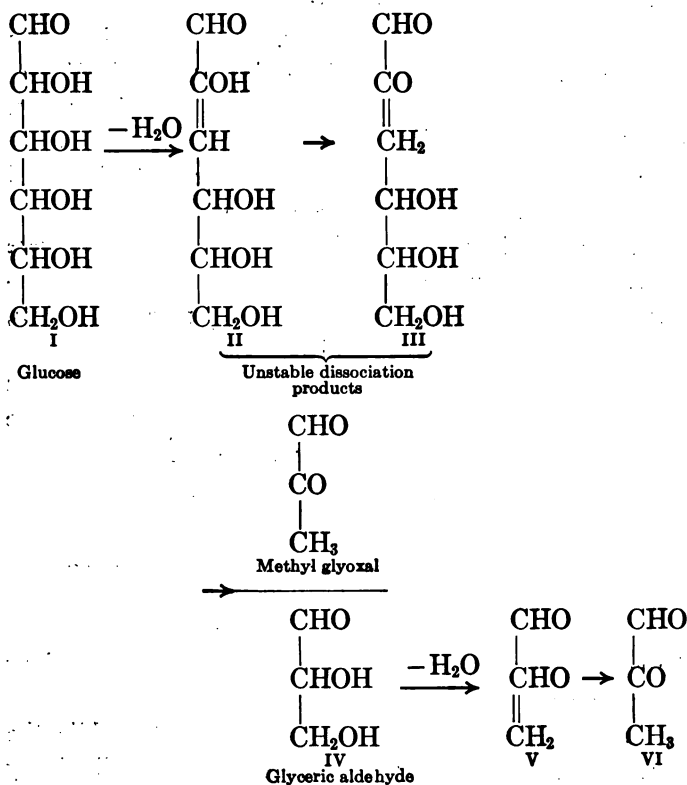
### THE CHEMICAL CHANGES IN THE FERMENTATION OF THE SUGARS

**164.** The nature of the chemical changes involved in the fermentation of sugars has been very carefully investigated, and the mechanism of the change of hexose into alcohol is fairly definitely understood. On the one hand the method of investigation consisted of the careful study of the compounds which result from the decomposition of glucose by chemical agents, especially alkalies, since they induce decompositions of a profound character resembling a certain type of fermentation (lactic acid). There is a certain degree of probability that the cleavage of the glucose molecule by alkalies will follow the same lines as those on which sugar normally tends to dissociate, and it is along these lines that the enzymes of the yeast accelerate change.

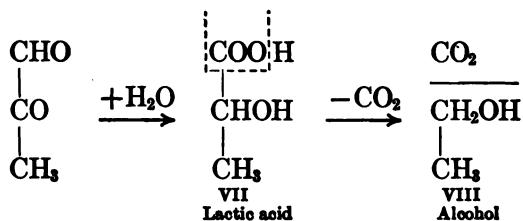
On the other hand the inquiry may be directed toward testing under carefully regulated conditions the ability of yeast to take any supposed intermediary product in the process of cleavage in fermentation and to complete the process of conversion of this into alcohol. Any compound which can be so converted is regarded as a possible intermediary product, and any one which cannot be converted into alcohol must be excluded.

Another procedure possible of application in certain instances is to conduct the trial with the yeast in the pres-

ence of some harmless substance which will combine with a supposed intermediary product whose existence in ordinary practice is but transient, and to remove it from the sphere of influence of the living organism, thus causing its accumulation. The results of extensive inquiry by many investigators have been the proposal of the following explanations of the process of fermentation :



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The central idea is the alternate dissociation and re-addition of the elements of water. When alkali acts on glucose, lactic acid is formed to the extent of 54 per cent of the theoretical amount, formic acid to .5-2 per cent, and 40 per cent of a mixture of hydroxy acids containing four and six carbon atoms. About 1 per cent of alcohol and  $\text{CO}_2$  are also formed. There is no glycolic or oxalic acid, nor glycol or glycerol formed. If lactic acid were formed by a separation of the carbon chain into two three-carbon aldehydes and subsequent oxidation and reduction, the resulting lactic acid should be optically active, which is not the case in lactic acid fermentation, and this lends support to the view that some three-carbon aldehyde other than glyceraldehyde is first formed.

Pyruvic acid,  $\text{CH}_3\text{—CO—COOH}$

Methyl glyoxal,  $\text{CH}_3\text{—CO—CHO}$

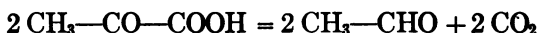
Glyceric aldehyde,  $\text{CH}_2\text{OH—CHOH—CHO}$

Dihydroxyacetone,  $\text{CH}_2\text{OH—CO—CH}_2\text{OH}$

have all been proposed as the most probable intermediary cleavage product.

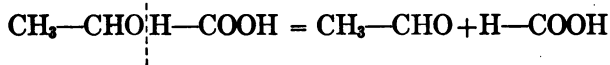
Methyl glyoxal is not fermentable by yeasts, while the results are positive for glyceraldehyde and dihydroxy

acetone. The most satisfactory explanation is probably the following :



This scheme receives strong support from the now well-substantiated observation that yeast juice free from living cells contains the enzyme, *carboxylase*, which accelerates the decomposition of pyruvic acid into acetaldehyde and carbon dioxide. Acetaldehyde is readily reduced to alcohol.

Another theory of alcoholic fermentation deserves to be mentioned. Schade showed that lactic acid treated with dilute sulphuric acid formed acetaldehyde and formic acid :

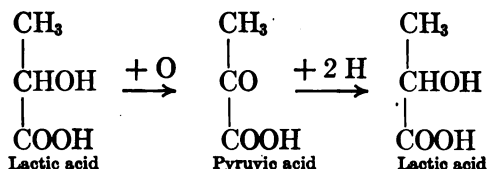


showing a tendency for this line of cleavage which might be accelerated by a yeast enzyme. Formic acid is rapidly decomposed catalytically by means of metallic rhodium into hydrogen and carbon dioxide. Schade held that the latter reaction might also be catalyzed by a ferment, thus producing through lactic acid as a first product from hexose, acetaldehyde, and hydrogen in a nascent state to reduce it, together with one molecule of carbon dioxide for each molecule of alcohol produced. This is the proportion actually observed in yeast fermentation. Yeasts do not however ferment a mixture of acetaldehyde and sodium formate.

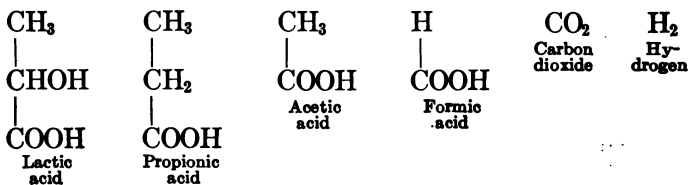


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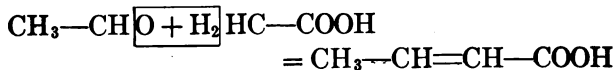
**Lactic Acid Fermentation** is equally in harmony with the assumption that pyruvic acid is first formed from hexose. Lactic acid can be oxidized to pyruvic acid or the latter reduced to lactic acid :



**Butyric Acid Fermentation.** — *Bacillus holobutyricus* has been shown capable of converting lactic acid into butyric acid in considerable amounts. The products are *n*-butyric acid, carbon dioxide, and hydrogen. The destruction of lactic acid by bacteria leads to the accumulation of appreciable amounts of the following products :



The most plausible explanation of butyric acid fermentation from lactic acid is that based on the condensation of acetaldehyde with acetic acid, analogous to the condensation of benzaldehyde with acetic acid to form cinnamic acid in Perkin's synthesis (207) :



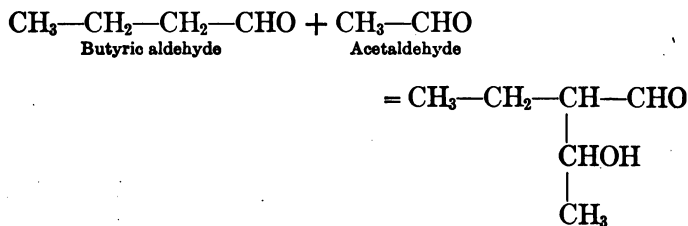
The resulting crotonic acid would be reduced to butyric acid.

# FORMATION OF FATTY ACIDS FROM CARBOHYDRATES

165. The nature of the process by which carbohydrate is changed into fatty acids for fat synthesis within the body is not fully understood. There is satisfactory experimental proof that pigs and geese have become fat at the expense of the carbohydrate moiety of the diet. A significant fact which any hypothesis must recognize is the existence among the ordinary fatty acids of those only which contain an even number of carbon atoms, chiefly 12, 14, 16, and 18 carbon atom acids. Myristic and palmitic acids with 14 and 16 carbon chains refute the supposition that three molecules of hexose condense to form a chain which by reduction of hydroxyls and oxidation of the terminal carbonyl could form a fatty acid.

An adequate explanation must account for the addition of two carbon atoms at a time to some of the lower members of the series, or to a compound which is readily oxidizable to a fatty acid.

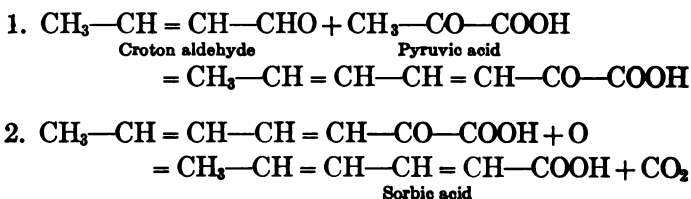
Lieben has shown that butyric aldehyde can condense with acetaldehyde in the presence of dilute alkali, but the resulting aldehyde is not a straight chain :



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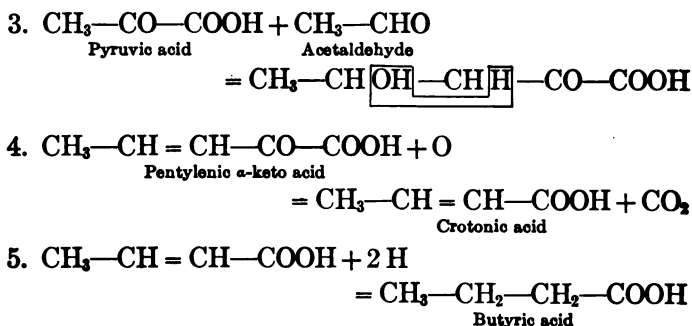
This cannot therefore be considered a very probable explanation of what takes place in the animal body.

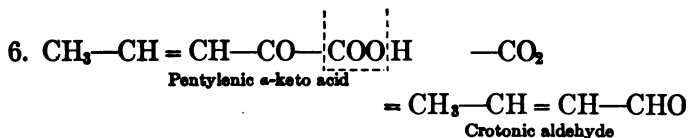
The most plausible hypothesis yet advanced concerning the biological method of forming fats is that of Smedley, who condensed croton aldehyde with pyruvic acid, and by oxidizing the resulting ketonic acid with hydrogen peroxide,  $\text{CO}_2$  was split off and the doubly unsaturated *sorbic acid* was formed :



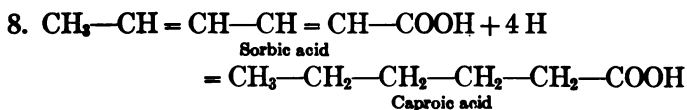
It is easy to understand how the double bonds could be removed from such an acid by reduction.

Smedley suggests pyruvic acid and acetaldehyde as the starting point for fat synthesis in the body. The following reactions will illustrate the process :





7. By reactions 1 and 2 sorbic acid is formed.



By an extension of this synthesis the higher fatty acids would result.

## CHAPTER XVII

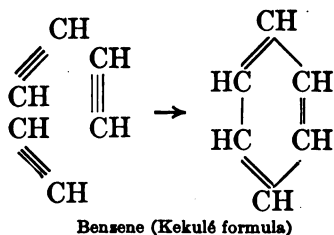
### THE AROMATIC COMPOUNDS

**166.** The hydrocarbons of the aliphatic series, or the fatty compounds, are not products of animal or plant metabolism, with the exception of methane, which results from the bacterial fermentation of cellulose. None of them have highly agreeable odors. There are in certain products of vegetable origin compounds which contain only carbon and hydrogen, and are very poor in hydrogen, suggesting compounds of a highly unsaturated character, as isoprene (82). These differ in every respect in their properties from the unsaturated or the saturated hydrocarbons of the aliphatic series. Thus *toluene*,  $C_7H_8$ , from Tolu balsam, and *cymene*,  $C_{10}H_{14}$ , from oil of eucalyptus, oil of thyme, oil of caraway, and other *essential oils*, are hydrocarbons of pronounced and characteristic aromatic odors. They do not form addition products with the halogens as do the unsaturated hydrocarbons. *Benzoic acid*, which is found in gum benzoin, in cranberries, and elsewhere in plants, yields when its calcium salt is subjected to dry distillation, a hydrocarbon,  $C_6H_6$ , *benzene*.

Toluene is oxidized to benzoic acid and is therefore closely related to benzene. Cymene yields on oxidation a dibasic acid, *teraphthalic acid*, which on distillation of its calcium salt likewise yields benzene.

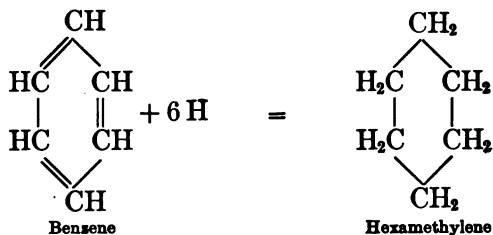
**Benzene** may be regarded as the mother substance of a large number of compounds of great biological and technical interest, and its chemistry should be considered in some detail. The constitution of its molecule was first suggested by Kekulé in 1867, and was based principally on the following evidence: Since benzene does not behave like an unsaturated compound, its structure must be of a special nature to account for this property, for it is not possible to write the formula  $C_6H_6$  as an open chain without the employment of double or triple bonds. It has therefore a closed ring structure.

Benzene is formed when acetylene is passed through a heated tube or subjected to high pressure. The molecular weight is 78, so it follows that in the polymerization three molecules of acetylene condense into one:



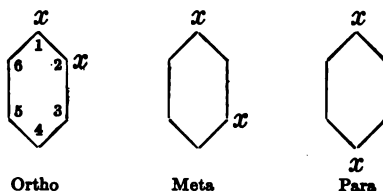
The correctness of the view that the benzene molecule represents a closed ring of six carbon items linked alternately by single and double bonds is supported by the observation that when the vapors of benzene mixed with hydrogen are passed through a heated tube containing finely divided nickel, six atoms of hydrogen are absorbed and hexamethylene (112) is formed:

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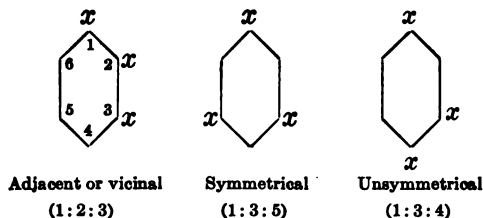
Kekulé also emphasized the fact that *all of the six hydrogen atoms of benzene are equal*, since each is attached to a carbon which is alternately singly and doubly bound, *i.e.* to carbon atoms which are alike. If this is true there should be but one mono-substitution product of benzene as chlor, brom, nitro, amino, etc., benzene, all of which derivatives are known. Actually but a single compound of these types is known. On the normal aliphatic hydrocarbon containing six carbon atoms, three isomeric mono-substitution products exist, depending on whether the substituting group is at 1, 2, or 3,  $\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}_1$

On the other hand, theory calls for three disubstitution products of such a hexagonal ring, and three dichlor, dinitro, dihydroxy, etc., benzenes, but no more than three, are known. These are called *ortho*-, *meta*-, and *para*- derivatives (designated as o-, m-, and p-) according



to whether the substituting groups occupy positions on neighboring carbon atoms (1:2) or on atoms separated by one (1:3) or by two carbon atoms (1:4) respectively. The position 1:5 is the same as 1:3 and 1:6 is the same as 1:2. The number of isomers should be the same for disubstitution products whether these are similar or dissimilar.

There should be, according to theory, three isomers of a trisubstitution product of benzene provided all substituting groups are similar, but more if two are similar and one dissimilar.



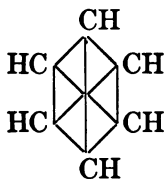
Of the vast number of derivatives of benzene which have been prepared and studied, theory has in all cases accorded with observation.

It is essential, if we accept this structure for benzene, to assume that the double bonds are alternating between the 1:6 and the 1:2 positions, otherwise there should be observed different properties for a disubstitution product in which the groups were separated by a single and double bond respectively. Such a vibration was assumed by Kekulé. To obviate this difficulty, since but one ortho disubstitution product has been observed, the *centric formula* was proposed by Armstrong. According



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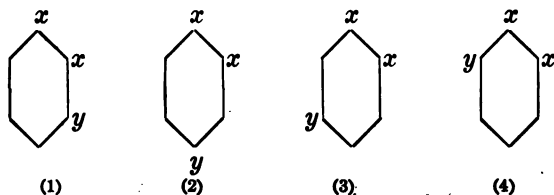
to his assumption the fourth bond of each carbon atom in the ring is directed toward the center:



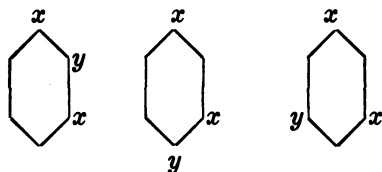
Such a structure accounts for the extreme stability of benzene, which is much greater than that of the aliphatic hydrocarbons, and also accounts for the peculiar isomerism of its derivatives and for its "aromatic" character. The six-membered ring is referred to as the benzene nucleus, and since many derivatives of benzene are known in which one or more aliphatic groups replace the hydrogen atoms of the nucleus, these are called "side chains." Substitution can be effected either in the nucleus or in the side chain.

#### DETERMINATION OF POSITION OF SUBSTITUTING GROUPS IN THE NUCLEUS

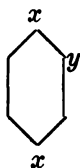
**167.** This has been determined by very extensive and elaborate study for a few substitution products of benzene by a method, the principle of which was enunciated by Körner. It depends upon the fact that when a third substituent *y* is introduced into an *ortho* compound, in which both substituting groups are similar, *but two isomers can be formed*. This is true whether *y* is like or unlike *x*:



Two and 3 are the same and 1 and 4 are the same. In the case of the *meta* compound *three isomers can be formed*:



While in the case of a *para* compound *but one* trisubstitution product can result:



No matter what position *y* may take, it occupies the same relative positions with respect to the other substituents, viz. it is always in the *ortho*-position to one and in the *meta* position to the other. The experimental evidence in support of the theory of structure consists in the preparation of compounds having the percentage composition called for by the theory and efforts to separate the product by crystallization, distillation, etc., into fractions

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which have the same composition, but different physical properties; *i.e.*, isomers. The fact that patient search has revealed the existence of all the isomers demanded by theory, *and in no instance more than these*, is convincing evidence of the validity of the theory.

**Benzene**,  $C_6H_6$ , is a colorless liquid with a characteristic odor, which boils at  $80^\circ$ . When strongly cooled it crystallizes, the crystals melting when warmed to  $5.4^\circ$ . Its specific gravity at  $20^\circ$  is .874. It burns with a smoky flame and its vapors are inflammable. It dissolves in all proportions in alcohol or ether, but is insoluble in water. It dissolves fats, resins, etc., and is a good solvent for sulphur, phosphorus, iodine, and many other substances.

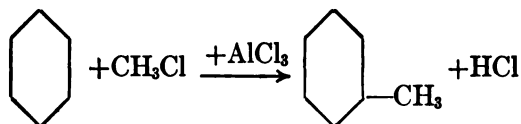
The benzene of commerce, also called *benzole*, was formerly obtained from coal tar, which on distillation yields in the fraction obtained up to  $150^\circ$ , from 3–5 per cent of a mixture of benzene and its homologues, *toluene* and *xylene*. Recently Rittmann has perfected a process by means of which the aliphatic hydrocarbons of petroleum can be made to yield 10–15 per cent of these cyclic hydrocarbons. This process consists in heating the petroleum under pressure for a time, and then distilling the product. The principle involved depends upon the *dissociation* of the aliphatic hydrocarbons under these conditions into various unsaturated hydrocarbons, among which are a small content of acetylene and of its alkyl derivatives (see p. 164). At high temperatures and pressures acetylene condenses to benzene, an irreversible reaction.

## PHYSIOLOGICAL PROPERTIES OF BENZENE

168. The aliphatic and aromatic hydrocarbons show considerable differences in their physiological properties. The lower members of the methane series produce sleep if inhaled, and death by asphyxia. The toxicity increases as the carbon atoms become more numerous. Hexane is actively intoxicant, producing a long stage of excitement followed by deep anæsthesia. It acts on the sensory side. Benzene and other aromatic hydrocarbons act principally on the motor centers, producing convulsions and paralysis. Benzene has furthermore a selective toxic effect for the white blood corpuscles, producing leucopenia, and is employed in medicine in cases of leucæmia.

## HOMOLOGUES OF BENZENE

169. Friedel and Crafts Reaction. When benzene is treated with an aliphatic halogen compound in the presence of aluminum chloride a reaction takes place in which hydrochloric acid gas is evolved and the aliphatic group is linked to the benzene nucleus:



For the sake of simplicity the hexagonal ring is employed to represent benzene.

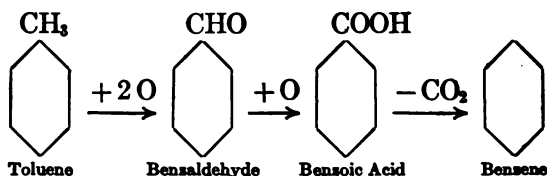
By the employment of the homologues of methyl chloride, ethyl, propyl, etc., groups can be substituted for a hydrogen atom in the benzene ring. The benzene nucleus

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less one hydrogen is called the *phenyl group*. Several of these compounds are of great importance, and their chemical behavior is of considerable interest.

**Toluene**,  $C_6H_5CH_3$ , is formed by the dry distillation of tolu balsam and of many resins. It occurs in coal tar and is separated from it by distillation along with benzene. It boils at  $110^\circ$  and by fractional distillation can be separated from benzene and other homologues. It is much employed as an antiseptic in biochemical work.

When oxidized by chromyl chloride,  $CrO_2Cl_2$ , it is converted by the oxidation of the "side chain," the methyl group, into an aldehyde,  $C_6H_5CHO$ , called *benzaldehyde*, which may be regarded as phenyl formaldehyde. More vigorous oxidizing agents convert toluene directly into benzoic acid,  $C_6H_5COOH$ , which is the acid corresponding to benzaldehyde. It may be regarded as phenyl formic acid. It has been noted that on heating the calcium salt of benzoic acid carbon dioxide is removed from the carboxyl group and benzene is formed. The following transformations for toluene illustrate the general behavior of the compounds containing both an aromatic and an aliphatic group:



Longer side chains as in ethyl-, propyl-, isopropyl-, etc., benzene oxidize, no matter how many carbon atoms con-

tained in them, into carboxyl. Hence the three derivatives just named all yield benzoic acid.

**170. Chlor toluenes.** It is obvious that derivatives of two types can be produced by the action of chlorine on toluene, viz. derivatives in which the chlorine occupies the *ortho*-, *meta*- or *para*- position to the methyl group in the benzene nucleus, or those in which one, two or three of the hydrogen atoms in the methyl group are replaced by chlorine. The position taken by chlorine when it reacts with toluene depends upon the conditions under which the reaction takes place. At low temperatures and in the absence of light *ortho*- and *para*-chlor toluenes are formed in about equal proportions, with very little of the *meta*- compound. When Cl acts on *p*-toluidine (176) the Cl enters the *m*- position to the CH<sub>3</sub> group. The action is greatly accelerated by the presence of halogen carriers, such as iodine, ferric chloride, antimony trichloride, etc.

At high temperatures (110°) even in the absence of light chlorine substitutes in the side chain exclusively. In the presence of halogen carriers, however, the chlorine enters the nucleus even at high temperatures.

At ordinary temperatures in direct sunlight the chlorine enters the side chain exclusively.

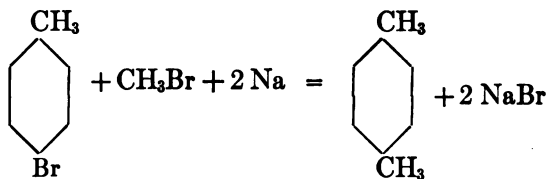
The terms chlor-, brom-, and iodo-toluenes refer to the *o*-, *m*-, *p*-, derivatives. The derivatives in which the halogen is in the side chain are named as follows:



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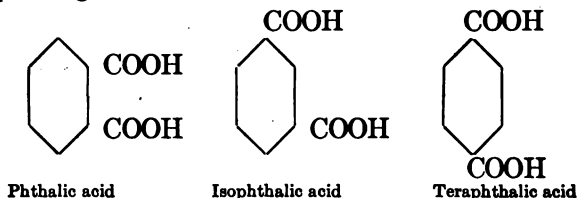
The group  $C_6H_5-CH_2-$  is called the benzyl-radical;  $C_6H_5CH =$  benzal-, and  $C_6H_5CH \equiv$  benzo-, radical. The behavior of these will be further described later.

**171. Xylenes.** Dimethyl, benzenes,  $C_6H_4(CH_3)_2$ , are formed by the Fittig reaction, employing brom toluenes and methyl bromide:



The same result is obtained by means of the Friedel and Crafts reaction (169), by means of which all of the hydrogens of the benzene nucleus have been successively replaced by methyl groups.

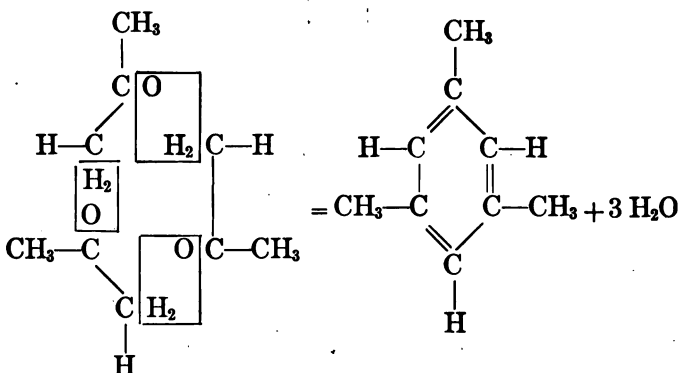
Ortho-, meta-, and para-xylenes can yield by oxidation either monobasic o-, m-, and p-toluic acids, or the three corresponding dibasic acids:



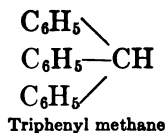
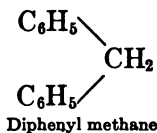
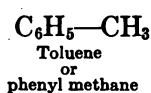
Phthalic acid when heated loses a molecule of water, forming an anhydride. This is employed extensively in the preparation of dyes.

**172. Mesitylene,** symmetrical trimethyl benzene,  $C_6H_3(CH_3)_3$ , is formed by methods analogous to the for-

mation of xylene (171), and also by the polymerization of acetone in the presence of strong sulphuric acid :



Another class of hydrocarbons is known in which two or three phenyl groups replace as many hydrogen atoms in the methane group :

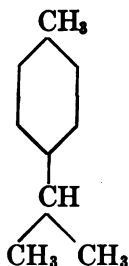


Diphenyl methane is formed by the interaction of benzyl chloride with benzene by the Friedel and Crafts reaction.

Triphenyl methane is prepared in large quantities in the dye industry from chloroform,  $\text{CHCl}_3$ , and benzene, likewise by the Friedel and Crafts reaction (169).

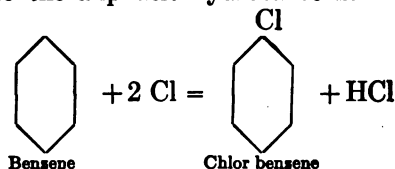
173. **Cymene**, or methyl-p-isopropyl benzene, occurs





in numerous essential oils. It yields successively on oxidation p-toluic acid and terephthalic acids (171).

**Halogen Derivatives of Benzene.** Chlorine acts upon benzene, substituting its hydrogen atoms in a manner analogous to the aliphatic hydrocarbons.



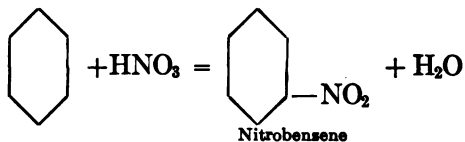
The action is greatly accelerated by the presence of iodine. This action is in part due to the fact that in the formation of iodine chlorides,  $\text{ICl}$  and  $\text{ICl}_3$ , the molecule of chlorine  $\text{Cl}_2$  is broken up with the formation of *nascent* chlorine; and in part to the instability of the chlorides of iodine which causes them to dissociate into active, *nascent*, chlorine. There will be in the system containing chlorine and iodine, some of the chlorides of iodine together with their dissociation products.

Bromine likewise acts directly on benzene with the evolution of hydrobromic acid gas. The action is greatly accelerated by the presence of metallic aluminum.

Benzene is not acted upon directly by iodine, but iodo benzene can be prepared from aniline by the diazo reaction (177).

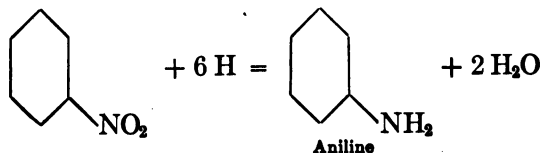
The halogen derivatives of benzene are more stable than the aliphatic halogen compounds. The halogen is not replaceable by other groups, as hydroxyl, etc.

**174. Nitrobenzene** is produced when concentrated nitric acid acts upon benzene. This action is in marked contrast to the behavior of the aliphatic compounds, which cannot be directly nitrated.



Nitrobenzene is a yellowish oily liquid, which crystallizes when cooled and melts at 3°. It boils without decomposition at 210°. It has the odor of bitter almonds and is employed as a scent for soap. It is but slightly soluble in water, but dissolves in alcohol and ether and in concentrated sulphuric acid. From the latter solution it is precipitated unchanged on dilution with water. Nitrobenzene is prepared on a large scale for the manufacture of aniline.

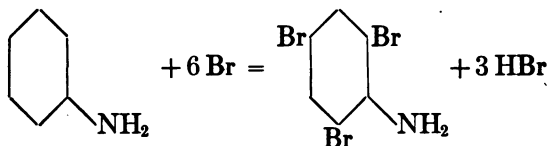
**175. Aniline**,  $\text{C}_6\text{H}_5\text{NH}_2$ , *aminobenzene*, results from the action of nascent hydrogen on nitrobenzene:



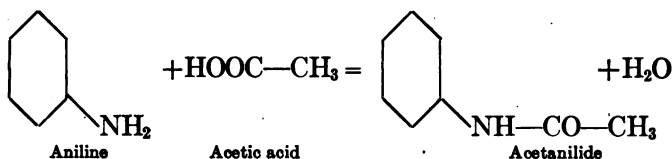
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Aniline may be regarded as a substituted ammonia. The benzene nucleus with one hydrogen atom removed is termed the *phenyl group* and is commonly abbreviated to  $C_6H_5-$  except where the illustration of structure is desired. Aniline may therefore be called *phenyl amine*. It is a weak base, but forms salts with acids. From these the free base is liberated by treatment with alkalis. It is appreciably soluble in water, and readily so in alcohol and ether. It has a characteristic odor and is highly toxic, producing muscular spasms of central origin and causing destruction of the red blood corpuscles.

The presence of an amino group on the benzene nucleus greatly increases the ease with which the other hydrogen atoms can be substituted. Thus bromine acts but slowly on benzene and by direct action the principal end-product is monobrom benzene, while it reacts readily with aniline, forming symmetrical tribrom aniline:

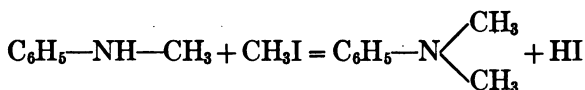
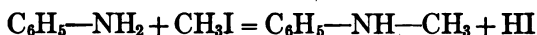


The favorable influence of the amino group on either halogenation or nitration is so great that in order to prepare the monobrom or mononitro aniline the amino group must be acetylated. This is effected by boiling aniline with glacial acetic acid. The acetyl group serves to "protect" the benzene nucleus:



*Acetanilide* is a colorless crystalline substance, which melts at  $116^\circ$  and boils at  $304^\circ$ . It is an important antipyretic. It is hydrolyzed into aniline and acetic acid.

**176. Alkyl Anilines.** Aniline will react with one or two molecules of alkyl halide to form alkyl anilines:



The dimethyl anilines are readily prepared by boiling aniline with methyl alcohol and hydrochloric acid. Methyl chloride is formed progressively as the reaction proceeds and uses it up. Other alkyl groups can be introduced into aniline by employing the corresponding alcohols.

The alkyl anilines are stronger bases than aniline.

The methyl derivatives of aniline in which the alkyl groups occupy a position on the benzene nucleus are known respectively as o-, m-, and p-toluidines.

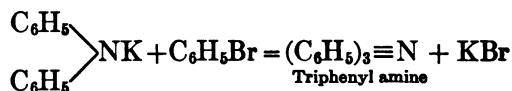
**Diphenyl Amine,**  $\text{C}_6\text{H}_5 \begin{array}{l} \diagup \\ \diagdown \end{array} \text{NH}$ , is a crystalline compound which melts at  $54^\circ$  and boils at  $310^\circ$ . It is prepared by

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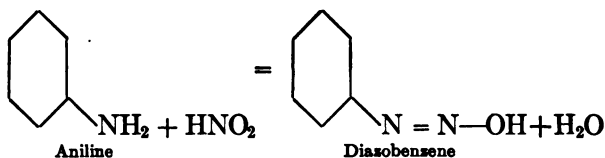
heating aniline hydrochloride with aniline under pressure at  $240^{\circ}$ :



Owing to the influence of the negative character of the phenyl groups the remaining hydrogen attached to the nitrogen in diphenyl amine behaves like acid hydrogen and is replaceable by metals. By heating the potassium compound of diphenyl amine with brom benzene, there is formed triphenyl amine:



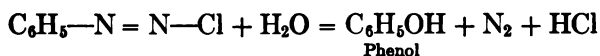
**177. Diazobenzene,  $\text{C}_6\text{H}_5\text{—N}=\text{N—OH}$ .** There is a very marked difference in the behavior of aniline, a primary amine of the aromatic series, and of the aliphatic primary amines. The former are converted into the corresponding alcohols (43), while the latter form *diazocompounds*:



Diazobenzene results from aniline. It behaves like a strong base and is unknown in the free state, since it is so unstable that it decomposes with an explosion. Its salts are crystalline and are safe only in a moist state, since they decompose violently when struck or heated. The

salts of diazobenzene with mineral acids are called diazonium salts. They are readily soluble in water, less soluble in alcohol, and are not soluble in ether.

An aqueous solution of a diazonium salt is decomposed on heating, with the formation of phenol :



This offers a ready means of replacing the amino group by hydroxyl on the benzene nucleus. Since nitro compounds are converted into amines by reduction, nitro groups are also replaceable indirectly by hydroxyl.

On boiling a diazonium salt with absolute alcohol, it is decomposed with the evolution of nitrogen and the formation of benzene :



The hydrogen is derived from the alcohol, a portion of which is converted into aldehyde :



In this case the diazonium group is replaced by hydrogen.

The diazonium group can also be replaced by halogen. Thus if a warm solution of potassium iodide is added to a solution of diazonium sulphate, iodobenzene is formed :



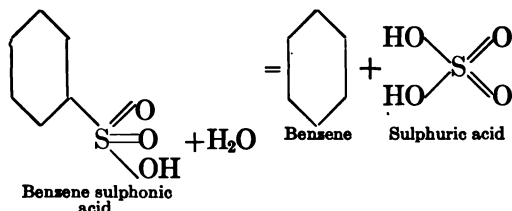
Similarly by adding cuprous chloride in concentrated hydrochloric acid, cuprous bromide in hydrobromic acid, or cuprous cyanide in potassium cyanide, to a solution of a benzene diazonium salt, chlor, brom, or cyano benzene respectively are formed. This is known as the *Sand-*

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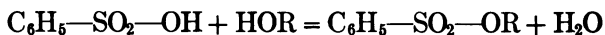
*meyer* reaction. It offers a ready means of synthesis for compounds which cannot be formed directly. Thus chlorine does not enter the *meta* position to the methyl group in toluene, but does in the chlorination of p-toluidine. The amino group can thereafter be removed by the diazo reaction, yielding meta-chlor-toluene.

**178. Benzene Sulphonic Acid**,  $C_6H_5-SO_3H$ , is formed by the action of concentrated sulphuric acid on benzene. It is a hygroscopic substance which melts at  $50^\circ$ . Its aqueous solutions are strongly acid and it forms salts which crystallize well.

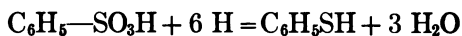
On heating with acids it is hydrolyzed into sulphuric acid and benzene.



Benzene sulphonie acid reacts with alcohols to form esters :



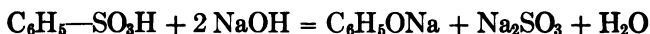
When subjected to the action of vigorous reducing agents it is reduced to phenyl mercaptan :



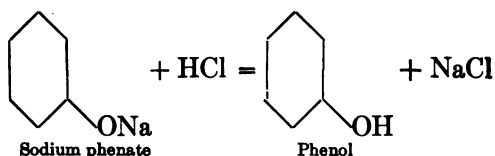
The hydroxyl of benzene sulphonie acid is replaced by chlorine when acted upon by phosphorus pentachloride, forming benzene sulphonyl chloride :



The salts of benzene sulphonic acid when fused with sodium hydroxide are decomposed into the metallic derivative of phenyl alcohol or *phenol*:



**179. Phenol**, or *carbolic acid*, is obtained by the action of acids on the sodium phenolate produced by the decomposition of benzene sulphonic acid by fusion with alkalis.



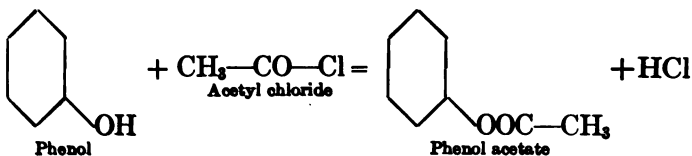
Phenol is present in coal tar and is obtained in the distillation of the latter. It is separated from hydrocarbons and basic compounds by the solubility of its sodium compound in water. Sodium phenolate or phenate is readily formed in aqueous solutions of sodium hydroxide. In this respect phenol shows properties markedly different from the alcohols of the aliphatic series. These are neutral in reaction and form metallic derivatives, the alcoholates, only in non-aqueous solutions and with the alkali metals. Phenol, while chemically a tertiary alcohol, has distinctly acid properties. It is not a sufficiently strong acid to react with carbonates, however, and while, *e.g.*, sodium phenolate is stable to water, it is decomposed by carbon dioxide.

As an alcohol phenol forms esters, but these are not readily formed by the direct heating of phenol with an

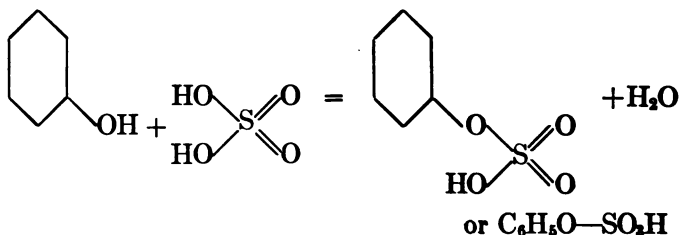


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acid. They are easily formed by the action of acid chlorides upon phenol or its salts :

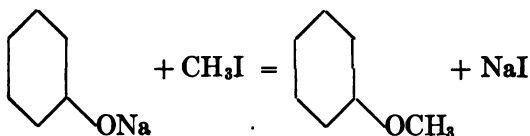


**180. Phenol Sulphuric Acid**, also called *phenyl sulphuric acid*, is formed in the animal body by the union of phenol with sulphuric acid. Since phenol is a product of the putrefaction of proteins by bacteria in the intestine, it is regularly absorbed to some extent. Phenyl sulphuric acid is therefore a regular constituent of the urine, and its amount depends upon the extent to which putrefaction goes on in the alimentary canal :



**181. Phenol Sulphonic Acids.** On dissolving phenol in concentrated sulphuric acid the sulphonic acid group is readily introduced into the benzene nucleus and *phenol sulphonic acids* are formed. The *o*- and *p*- derivatives are thus obtained. When two sulphonyl groups are introduced into benzene they take the meta position and on fusion with potassium hydroxide one is replaced by hydroxyl, forming *m*-phenol sulphonic acid.

**182. Phenol Ethers.** Phenol also forms ethers, but not readily by the direct action of phenol with an alcohol. They are easily produced by the action of alkyl iodides upon the phenolates (also called phenates) :



Phenol when pure is a colorless crystalline compound which is very deliquescent and turns pink on contact with the light and air. It is volatile with steam, melts at  $42^\circ$ , and boils at  $182^\circ$ . Its specific gravity at 0 is 1.084°. Its odor is characteristic, and it is highly toxic and corrosive, the latter action being due to its great affinity for water. One part of phenol dissolves in fifteen parts of water. It is much more soluble in alcohol. It is an excellent antiseptic.

Phenol can be formed by the direct oxidation of benzene in the presence of palladium black or aluminum chloride.

Like aniline, phenol is readily brominated. When bromine water is added to a solution of phenol, symmetrical tribrom phenol, a very insoluble compound, crystallizes out. This compound has served for the quantitative estimation of phenol. Phenol in water gives a violet coloration on adding a few drops of a solution of ferric chloride.

**183. Cresols,**  $\text{C}_6\text{H}_5$   $\begin{array}{l} \text{CH}_3 \\ \text{OH} \end{array}$ . There are three homologues

of phenol, the o-, m-, and p-, methyl phenols or cresols.

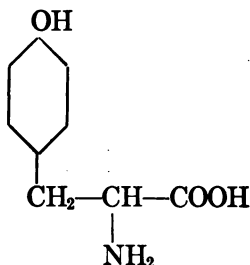
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They all occur in the distillate from coal tar. They possess antiseptic properties and are much employed in disinfection. When pure they are crystalline solids. o-cresol melts at  $31^{\circ}$ , the m- and p-cresols at  $5^{\circ}$  and  $36^{\circ}$  respectively. Like phenol they give a coloration with ferric chloride and are readily brominated and nitrated.

**184. Picric Acid.** Nitric acid acts energetically on phenol, forming symmetrical trinitro phenol, or *picric acid*. The latter compound is also formed by the action of nitric acid upon various substances, containing proteins, since the phenyl and phenol groups are contained in two of the amino acids found in nature, viz. phenyl alanine and tyrosine. Picric acid is a bright yellow crystalline substance of strongly acid character. The introduction of negative groups, as halogens, or nitro groups, into phenol increases its acid character, while the introduction of basic groups, as  $\text{NH}_2$ , depresses the acid character.

Picric acid forms readily crystallizing salts of slight solubility with many natural bases and is of great importance in the isolation and purification of these. It melts at  $122^{\circ}$  and can be sublimed without decomposition, but is explosive, owing to the large amount of oxygen contained within its molecule, which makes possible its complete and sudden self-oxidation. The salts of picric acid are much more explosive, decomposing with violence when heated or struck.

**185. Tyrosine**,  $\alpha$ -amino,  $\beta$ -oxyphenyl propionic acid, or *para-oxyphenyl alanine*:

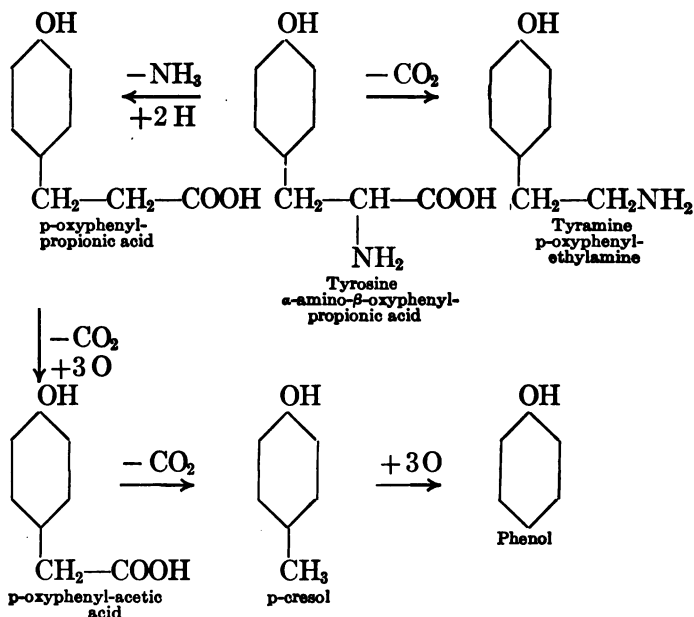


is a constituent of many proteins, and was first isolated by Liebig in 1846. It is set free from its union with other amino acids during the digestion of the proteins, and is also formed by boiling proteins with mineral acids. It is not present in gelatin, and the best yield is obtained from the hydrolysis of silk. With the other amino acids it is always present in the blood in minute amounts. Tyrosine is a colorless compound forming long silky needles which are but slightly soluble in cold water, but more easily in hot. Dilute acids or alkalies dissolve it, and on neutralizing the solutions, it crystallizes out. It gives a red color with a solution of mercuric nitrate in nitric acid, containing some nitrous acid. This is the *Millons* reaction, which has long served as a qualitative test for proteins. Gelatin when pure does not respond to this test. This color reaction is also given by phenol and other phenyl derivatives containing a hydroxyl group attached to the benzene nucleus.

Tyrosine is apparently one of the amino acids which is indispensable from the diet. On being acted upon by anaërobic bacteria the alanine complex is removed and phenol formed. Tyrosine is the source of the phenol

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formed by putrefactive action in the intestine. The transformations involved are illustrated by the following :

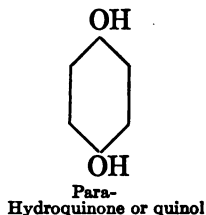
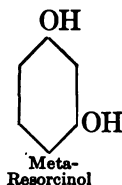
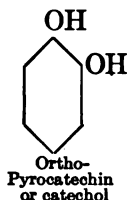


These changes are the result of the power of bacteria to remove  $\text{CO}_2$  from the carboxyl group in a manner analogous to that of the enzyme carboxylase on pyruvic acid ; to remove the amino group from amino acids as ammonia ; and to oxidize aliphatic side chains.

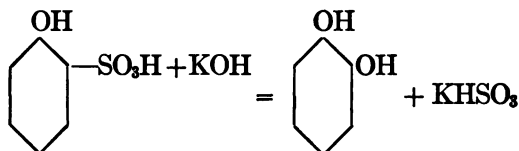
186. Tyramine,  $\text{C}_6\text{H}_4 \begin{array}{l} \text{OH} \\ \diagup \\ \text{CH}_2\text{CH}_2\text{NH}_2 \end{array}$ , or p-oxyphenyl-ethylamine, is a substance of mild toxicity occurring in putrefaction mixtures. Doses of 1-2 mg. injected intra-

venously cause a sudden and pronounced rise in blood pressure which soon passes away. The absorption of this compound from the intestine is possibly in part responsible for high blood pressure in certain individuals.

**187. Dihydroxy Benzenes.**—The three dihydroxy benzenes occur among natural products:

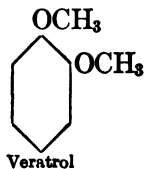
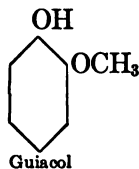


**188. Pyrocatechin**, o-dihydroxy benzene,  $C_6H_4(OH)_2$ , is obtained by fusing o-phenol sulphonic acid with potassium hydroxide:



It is a colorless crystalline compound melting at  $104^\circ$ . It occurs in the resin *catechu* and in beech wood tar.

**189. Guaiacol** and **Veratrol** are the monomethyl and the dimethyl ethers respectively of pyrocatechin.



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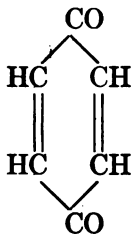
The former is found in beech wood tar and the latter in the seeds of *Sabadilla officinalis*.

**190. Resorcinol**, *m*-dihydroxy benzene,  $C_6H_4(OH)_2$ , is obtained from benzene *m*-disulphonic acid by fusion with potassium hydroxide at high temperatures. It is a colorless crystalline compound which melts at  $119^\circ$  and is somewhat volatile with steam. It has not been found in nature, but results from the fusion of various plant tissues with alkali. Its homologue, methyl resorcinol *orcin* (*m*-dihydroxy toluene), occurs in certain mosses.

Resorcinol is largely used for the preparation of the dye *eosin*.

**191. Hydroquinone**, *p*-dihydroxy benzene,  $C_6H_4(OH)_2$ , occurs as a glucoside *arbutin* which is widely distributed in plants of the family Ericaceæ. It is crystalline and melts at  $170^\circ$ . It is difficultly soluble in the ordinary solvents.

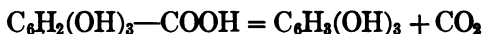
**192. Quinone** is formed by the oxidation of aniline



with chromic acid. It is an evil-smelling substance, easily volatile with steam. Easily soluble in hot water and in organic solvents. It is converted into hydroquinone on reduction. Quinone forms golden yellow crystals which melt at  $116^\circ$ .

## TRIHYDROXY BENZENES

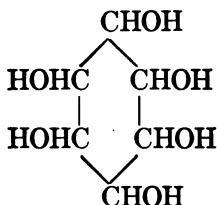
**193. Pyrogallol:** 1,2,3 *trihydroxy benzene*,  $C_6H_3(OH)_3$ , is formed by the distillation of gallic acid (212).



Its alkali salts absorb oxygen readily, and its solution in sodium hydroxide is employed in gas analysis for this purpose. The compound is oxidized and carbon monoxide is liberated as one of the decomposition products. It is employed as a developer in photography.

**194. Phloroglucin,** 1,3,5 *trihydroxy benzene*,  $C_6H_3(OH)_3$ , is prepared by the oxidation of resorcinol. It crystallizes from water, and melts at  $217^\circ$ . It gives a blue violet color with ferric chloride.

**195. Inosite,**  $C_6H_{12}O_6$ , occurs in nature in several isomeric forms. It is a derivative of the reduced benzene ring, hexamethylene, and is hexahydroxy benzene:

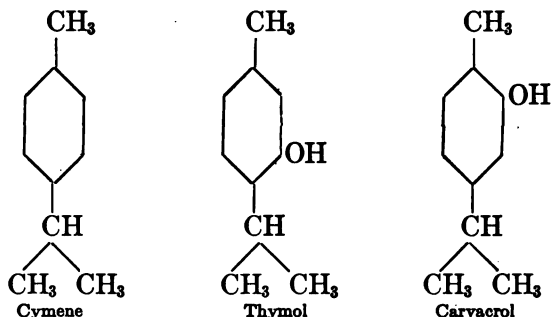


Inosite is found in heart muscle, in the brain, and is widely distributed in plants, especially in beans and peas in the unripe state. Its hexaphosphoric acid ester is called phytic acid, and is present in considerable amount in wheat bran and is a common constituent of plants.



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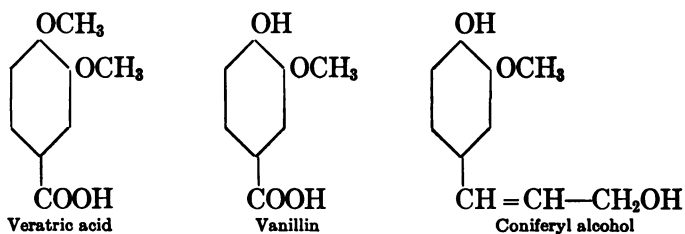
196. Thymol and Carvacrol are naturally occurring *methyl-isopropyl phenols*. They are derivatives of cymene.



Thymol and carvacrol are found in many plants. They have a very pleasant mint-like odor and possess mild antiseptic action.

197. **Protocatechuic Acid**, *catechol carboxylic acid*, results from the fusion of many resins with alkali. It is readily soluble in water and melts at 199°.

198. **Veratric Acid, Vanillin, and Coniferyl Alcohol.**—

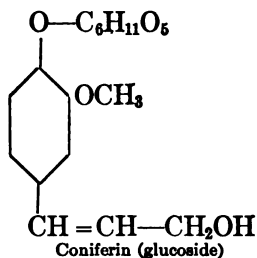


*Veratric acid*, the dimethyl ester of protocatechuic acid, occurs in the seeds of *Veratrum Sabadilla*.

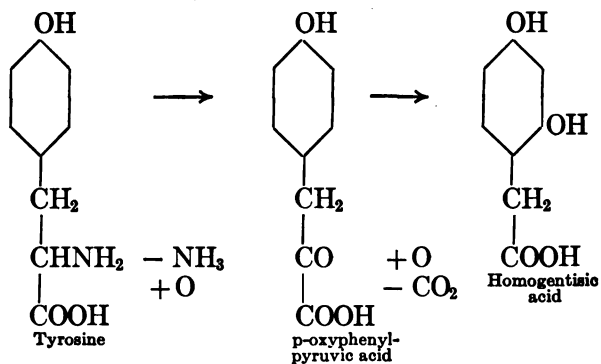
*Vanillin* is the substance giving the pleasant odor to

the vanilla bean. It is obtained by the oxidation of coniferyl alcohol.

*Coniferyl alcohol* occurs in coniferin, a glucoside found in the cambium sap of all coniferæ and in other plants.

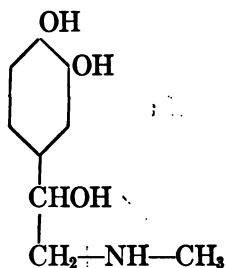


**199. Homogentisic, quinol acetic acid**, is a constituent of the urine in a type of abnormal metabolism known as alkaptonuria. The normal animal body is capable of the complete oxidation of the benzene ring when it is introduced in the form of tyrosine or phenyl alanine, but there is an anomaly of metabolism in which the later steps in the process fail. The mode of formation of homogentisic acid from tyrosine is probably as follows:

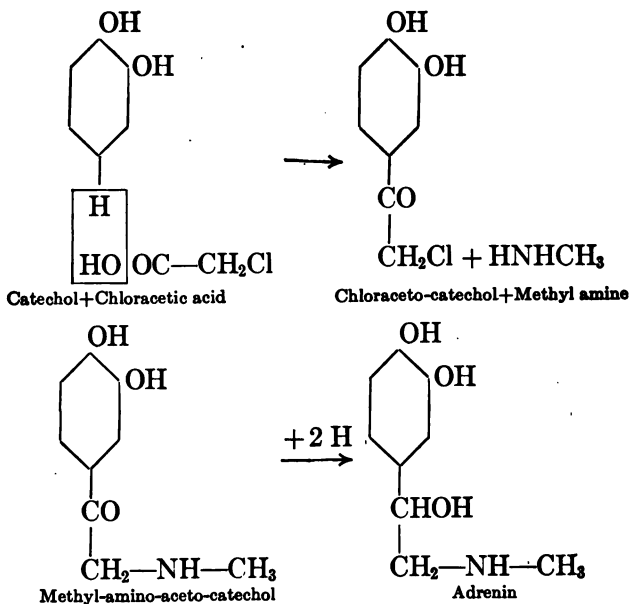


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### 200. Adrenin,



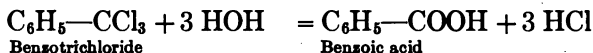
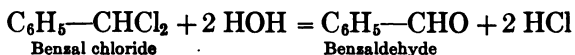
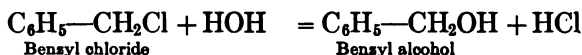
is the active principle of the adrenal glands, and one of the endogenous hormones, *i.e.* chemical regulators of metabolism. It has been produced synthetically by the following reactions :



The synthetic product is optically inactive, but has been resolved into its optical components. The natural product is levorotatory and greatly surpasses the dextro form in physiological activity. Adrenin produces a marked rise of blood pressure through a constriction of the blood vessels.

**201. Benzoic Acid**,  $C_6H_5COOH$ , is formed by the oxidation of toluol and its homologues containing longer side chains. It is found in gum benzoin, and other resins. In gum benzoin it is present chiefly as its ester, with benzyl alcohol as benzoate. It occurs also in cranberries.

Benzoic acid is formed from benzotrichloride by boiling with water. The behavior of the three chlor toluenes in which the chlorine is in the side chain, when boiled with water, is of synthetic interest:

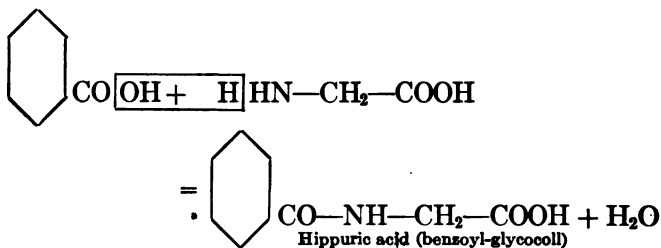


Benzoic acid results from the oxidation of either benzaldehyde or of benzyl alcohol with benzaldehyde as an intermediate product. The acid can also be formed by the hydrolysis of phenyl nitrile (177).

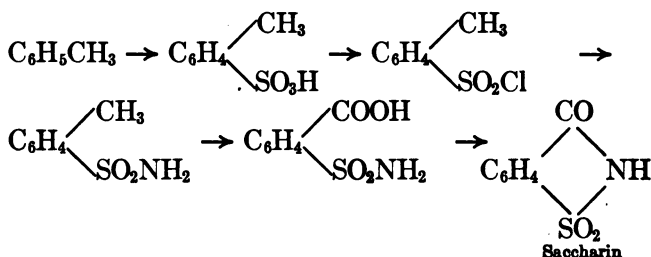
Benzoic acid has all the ordinary properties of an acid, forming salts, esters, etc. It is a colorless crystalline compound which is fairly readily soluble in hot water, but very slightly soluble in cold (1 part in 400).

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*Physiological Properties.* Benzoic acid has very little toxicity, large doses not being followed by any appreciable effects. Within the tissues it undergoes conjugation with glycocoll to form *hippuric acid*:



**Saccharin** is a derivative of o-sulphobenzoic acid, which is of particular interest because of its extreme sweetness. It is about 500 times sweeter than cane sugar, and has been employed to a considerable extent as an adulterant of foodstuffs in place of sugar, which is more expensive. The following reactions show the method of synthesis:



**202. Hippuric Acid (201)** is normally found in very small amount in the urine especially of the herbivora. It is not, however, a product of metabolism, but is present there because the foodstuffs of the herbivorous animal,

and to a less extent of the omnivora, contain substances which are oxidized to benzoic acid in the tissues.

Hippuric acid is not very soluble in cold water and less so in hydrochloric acid; and if much is present in the urine, it will crystallize out on acidifying with hydrochloric acid or better with the addition of ammonium sulphate. Glycocoll therefore serves as a protective substance against the foreign substance, benzoic acid.

**203. Benzyl Alcohol**,  $C_6H_5CH_2OH$ , occurs as such and also in ester combination with benzoic and cinnamic acid (207), in Tolu balsam, Peru balsam, and in the resin storax. It is isomeric with the cresols (183). Benzyl alcohol is formed by the method described in (201), and by the reduction of benzaldehyde. It is a liquid which boils at  $206^\circ$ , sparingly soluble in water, but more readily in alcohol and ether. It has all the typical properties of the alcohols.

**204. Benzaldehyde**,  $C_6H_5CHO$ , is found in the glucoside *amygdalin* from bitter almonds, where it is in union with two molecules of glucose and one of hydrocyanic acid.

For its preparation from benzal chloride see (201). It is a colorless liquid with the odor of bitter almonds. It boils at  $179^\circ$ , is very slightly soluble in water, but readily in alcohol and ether. It behaves in most respects like the aliphatic aldehydes, but differs from these in the following respects:

It does not reduce Fehling's solution or ammoniacal silver solutions. It does not polymerize, and when heated with alkalis one molecule is reduced to benzaldehyde and another is simultaneously oxidized to benzoic acid (p. 61).

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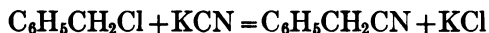
On shaking an alcoholic solution of benzaldehyde with potassium cyanide two molecules condense to form the ketone alcohol *benzoin*. Benzaldehyde yields nitro derivatives, sulphonic acids, etc. o-nitrobenzaldehyde condenses with acetone to form indigo blue.

### PHENYL FATTY ACIDS

**205. Phenyl Acetic Acid** is formed in small amounts in putrefaction of proteins. It is closely related to mandelic acid, the nitrile of which occurs in amygdalin:

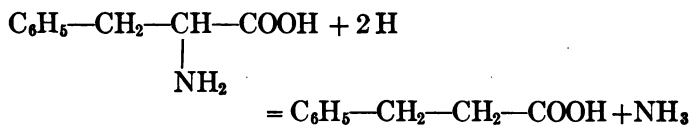


Its nitrile is formed from benzyl chloride by the action of potassium cyanide:



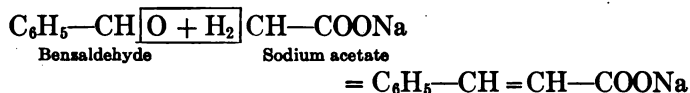
**206. Phenyl Amino Propionic Acid**,  $\text{C}_6\text{H}_5\text{—CH}_2\text{—CH—COOH}$ , or *phenyl alanine*, is a constant constituent

$\begin{array}{c} | \\ \text{NH}_2 \end{array}$   
of proteins. On putrefaction it gives rise to phenyl propionic acid:



Phenyl alanine is not readily isolated from among the products of hydrolysis of proteins. The form which occurs in nature is levorotatory. It is crystalline and melts at 275–280°.

**207. Cinnamic Acid**,  $\text{C}_6\text{H}_5\text{—CH=CH—COOH}$ , phenyl acrylic acid, is found in the resin storax. It is the most important phenyl derivative containing an unsaturated side chain. A synthesis described by Perkin is of unusual interest. Benzaldehyde condenses with sodium acetate when the two are heated together in the presence of a dehydrating agent (acetic anhydride).

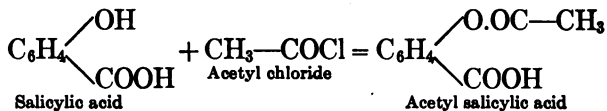


Alcohol, aldehyde and acid derivatives of phenol are also found in nature. The first of these is represented by saligenin, which occurs in the glucoside *salicin* in willow bark. It is a crystalline solid easily soluble in water and melting at  $82^\circ$ . The phenol group is in the ortho position.

**208. Salicylic Aldehyde**,  $\text{C}_6\text{H}_4 \begin{array}{l} \text{OH} \\ \text{CHO} \end{array}$ . The ortho-compound is found in certain volatile oils.

**209. Salicylic Acids**. —  $\text{C}_6\text{H}_4 \begin{array}{l} \text{OH} \\ \text{COOH} \end{array}$ . The ortho-compound is of greatest importance. It occurs as the methyl ester in oil of wintergreen, and the acid is likewise found in the flowers of *Spiræa*.

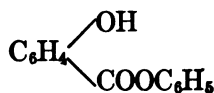
**210. Aspirin** is acetyl salicylic acid:

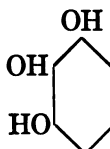




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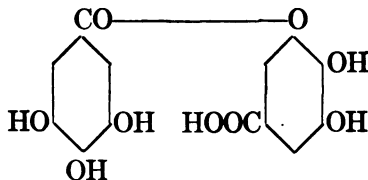
**211.** Salol is phenyl salicylate :



**212.** Gallic Acid, , is found in many

plants, as gall nuts, tea, etc. It is formed when tannin is hydrolyzed. It is a crystalline compound melting at  $220^\circ$ . It gives the same reaction with ferric chloride as does pyrogallol.

**213.** Tannic Acid, or *digallic acid*,

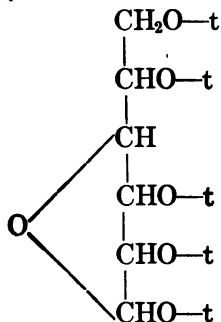


Tannic acid

is an ester formed between two molecules of gallic acid. It occurs in gall nuts, sumach, and other barks.

**214.** Tannins are of several varieties, distinguished by the color reactions which they give with various reagents. There are distinguished two general classes, the pyrogallol and the catechol varieties. The former give a dark blue color with ferric salts (ink) and the latter a greenish black. The latter forms a dark red ring at the juncture of the liquids when its solutions are treated with concentrated sulphuric acid.

Tannin on hydrolysis yields 7-8 per cent of glucose, and gallic acid. Its constitution has not been determined with certainty, but it is in some samples the penta digallic ester of glucose:

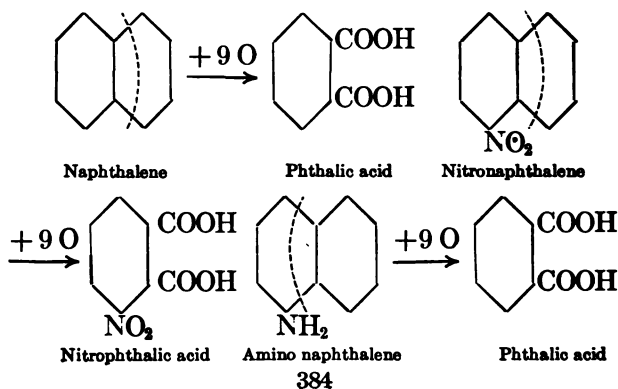


t represents digallic or tannic acid in this formula. One of the tannins recently synthesized by Fischer has nearly double the molecular weight of the most highly complex compound hitherto synthesized.

## CHAPTER XVIII

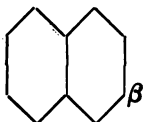
### CONDENSED BENZENE RINGS

**215. Naphthalene**,  $C_{10}H_8$ , is present in considerable amount in coal tar. Its structure is made clear by the behavior of its nitro and amino derivatives on oxidation. Naphthalene on oxidation yields phthalic acid (171), which shows that it contains a benzene nucleus and two substituting groups in the ortho position. On oxidizing the nitro compound, nitrophthalic acid is formed. When the nitro group is reduced to an amino group and the *naphthyl amine* oxidized, phthalic acid is formed. The molecule must therefore consist of two benzene rings having two carbon atoms in common :

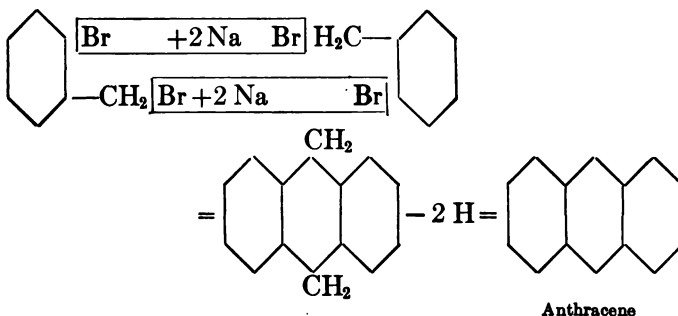


Naphthalene derivatives are extensively employed in the manufacture of dyes.

Naphthalene yields two mono substitution products  $\alpha$ - and  $\beta$ -:



**216. Anthracene**,  $C_{14}H_{10}$ , is formed by the Fittig synthesis from  $\alpha$ -brom benzyl bromide, with subsequent oxidation:

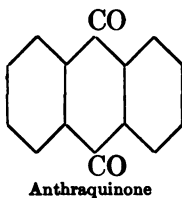


The structure of an anthracene derivative is arrived at through a study of the structure of its simpler oxidation products.

Anthracene is a constituent of coal tar, and is the mother substance of the red dye derived from the madder root. It is a colorless crystalline solid with a blue fluorescence, which melts at  $213^\circ$  and boils at  $351^\circ$ . It is easily soluble in benzene but difficultly in water, alcohol, and ether.

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Nitric acid oxidizes anthracene to *anthraquinone*, a pale

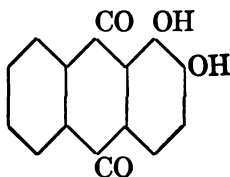


yellow crystalline substance with the nature of a ketone. It is used in making the dye *alizerin*.

## CHAPTER XIX

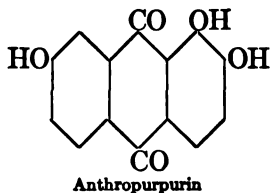
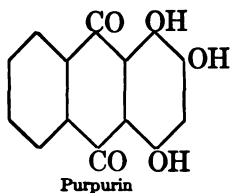
### ALIZERIN DYES

**217. Alizerin** occurs in the madder root in the form of a glucoside, *ruberythric acid*. It is hydrolyzed by an enzyme in the plant or by dilute acids, forming glucose and the dye "Turkey red." It is now made from anthraquinone. Its structure is :

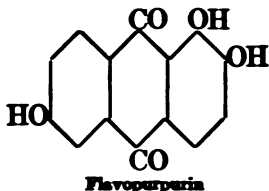


The hydroxyl groups are introduced by first making the sulphonic acid derivative by the direct action of  $\text{H}_2\text{SO}_4$  and then heating with sodium hydroxide (178).

Other alizerin dyes are :



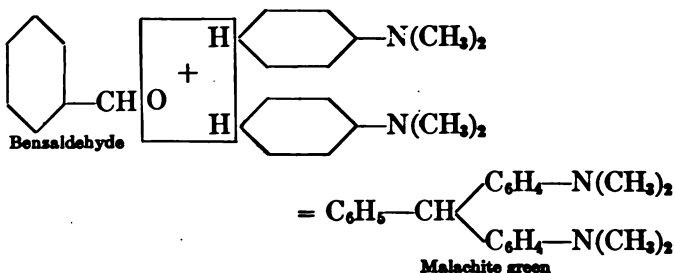
## 388 Organic Chemistry for Students of Medicine



Only those phenol derivatives of anthracene containing two hydroxyls in the ortho position to each other are dyes.

### THE TRIPHENYL METHANE DYES

**218. Malachite Green** is formed by heating benzaldehyde with dimethyl aniline and a dehydrating agent ( $\text{ZnCl}_2$ ).

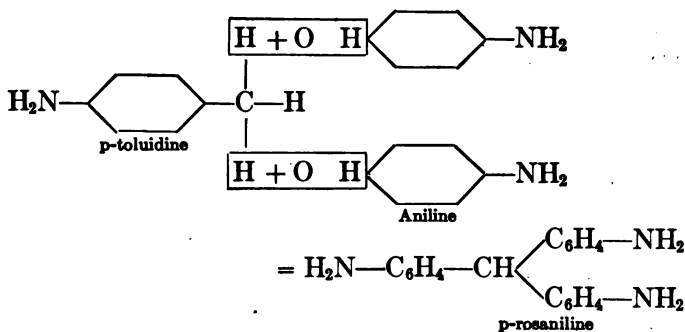


It is an excellent dye for silk and wool, but for dyeing cotton a mordant is required.

**Brilliant Green** is prepared in the same way as is malachite green, but diethyl aniline is employed.

**Acid Green** is also analogous to malachite green except that ethylbenzylaniline is employed.

**Pararosaniline** is prepared from p-toluidine and aniline by the action of an oxidizing agent:

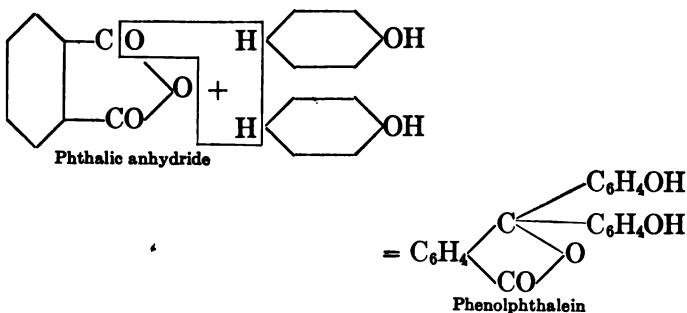


**Rosaniline**, *fuchsine*, or *magenta*, is prepared from a mixture of p-toluidine, o-toluidine, and aniline in an analogous manner.

Rosaniline and pararosaniline are reddish-blue dyes and can be converted into dyes having a bluer tint by methylation with methyl iodide (176).

Ethylation of the amino groups forms deeper blue dyes, while phenylation forms a pure blue dye known as *aniline blue*.

**Phenolphthalein** is another triphenyl methane derivative formed from phenol and phthalic anhydride:



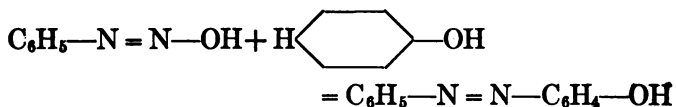
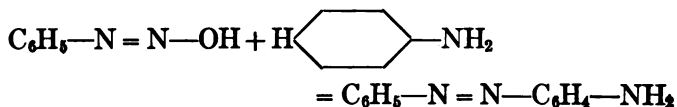


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Fluorescein, eosin, erythrosin, and many other dyes are derivatives of triphenyl methane.

#### THE AZO DYES

219. By substituting the hydroxyl of diazo-benzene (177) by amines, phenols, etc., a great number of dyes of both basic (from amines) and acid (from phenols) character have been produced :

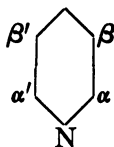
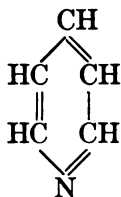


Congo red, bismarek brown, chrysoidin, helianthin, resorcin yellow, belong to this class.

## CHAPTER XX

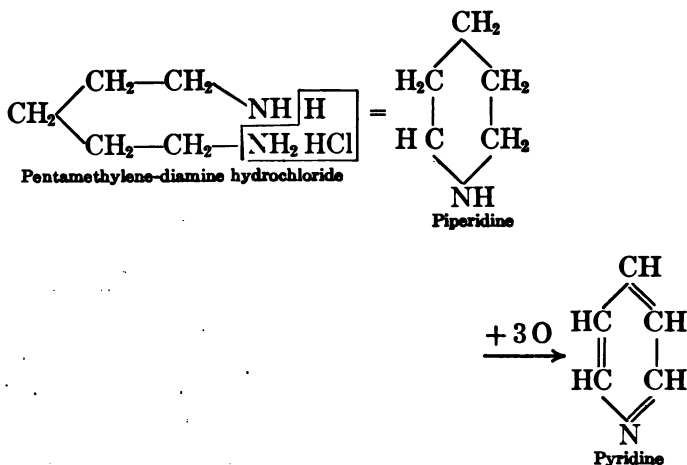
### HETEROCYCLIC COMPOUNDS

220. Pyrrole, pyrimidines, and imidazoles have been already described as representing compounds of cyclic structure in which both carbon and nitrogen were present. It remains to describe the six-membered ring containing five carbon atoms and one nitrogen. The simplest member of this group is pyridine. Neither pyridine nor its derivatives play a rôle in the biological processes of animal life as do the heterocyclic compounds mentioned above, but it is found widely distributed in plants, especially in the alkaloids. Pyridine itself is a highly toxic substance. It is represented as follows:



Its structure is arrived at by a method for its formation. Pentamethylene diamine (74) hydrochloride on dry distillation loses a molecule of ammonium chloride with the formation of the reduced cyclic structure *piperidine* which on oxidation yields pyridine:

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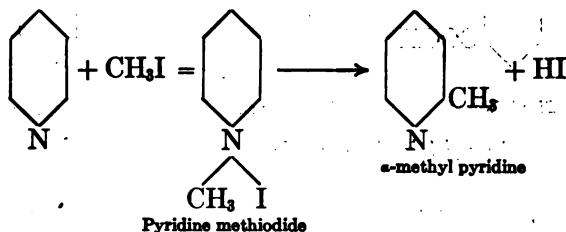
Pyridine and certain of its homologues are present in coal tar, and in "Dippel's Oil," the foul-smelling product of the dry distillation of bones.

Pyridine is a colorless liquid with the odor of tobacco smoke. It is a strongly alkaline substance which mixes with water in all proportions. It boils at 115°. It is one of the most stable of organic substances, being unattacked by boiling nitric or chromic acid. With sulphuric acid it reacts, forming a sulphonic acid. Halogens scarcely attack it. On heating pyridine with hydriodic acid at 300° it is destroyed, yielding normal pentane and ammonia.

Pyridine forms salts with acids. It does not form a nitroso derivative with nitrous acid.

As a tertiary amine pyridine combines with alkyl halides. These show an interesting rearrangement when heated,

the alkyl group changing its position from the nitrogen to the  $\alpha$ -carbon atom.



A delicate test for pyridine consists in heating the substance to be tested with a few drops of methyl iodide, then adding a small quantity of solid potassium hydroxide and heating again. Methyl pyridine hydroxide, having an extremely disagreeable odor, is formed when pyridine is present.

Piperidine,  $\text{C}_5\text{H}_{10}\text{NH}$ , is formed by heating the hydrochloride of pentamethylene diamine (74) or by the reduction of pyridine with sodium and alcohol. It behaves like a secondary amine in forming a nitroso derivative when treated with nitrous acid.

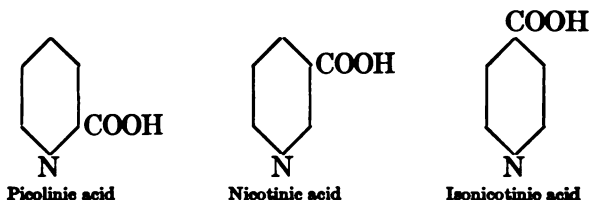
Piperidine occurs as a constituent of the alkaloid piperine found in pepper. It is a strong base, which boils at  $106^\circ$ .

#### HOMOLOGUES OF PYRIDINE

The methyl pyridines are known as *picolines*; the dimethyl pyridines, as *lutidines*; and the trimethyl pyridines, as *collidines*. Their properties are closely similar to those of pyridine.

**221. Nicotinic Acid** is the  $\beta$ -pyridine carboxylic acid:

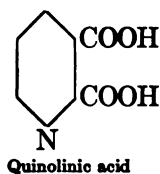
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Nicotinic acid is derived from the alkaloid nicotine by oxidation.

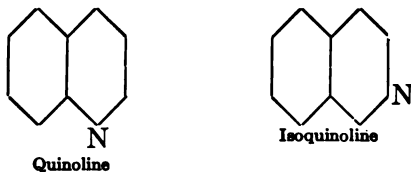
Picolinic acid is distinguished from the other isomeric acids by its property of giving a red color with ferrous sulphate.

Quinolinic Acid is an  $\alpha$ - $\beta$ -dicarboxy pyridine. At  $190^{\circ}$

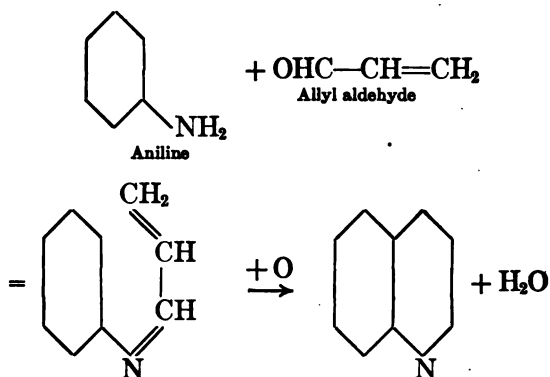


it loses carbon dioxide and is converted into nicotinic acid.

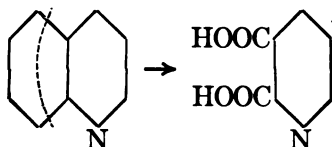
**222. Quinoline** is a compound containing a benzene ring condensed with a pyridine ring :



Both isomers occur in coal tar, but quinoline is usually prepared by synthesis. Its structure is made clear by its synthesis from allyl aniline by oxidation :



and further by the fact that quinoline yields on oxidation quinolinic acid :



It is a colorless liquid of an oily consistency which boils at  $239^{\circ}$  and has a characteristic rather pleasant smell.

Isoquinoline closely resembles quinoline, but is a solid which melts at 23° and boils at 241°.

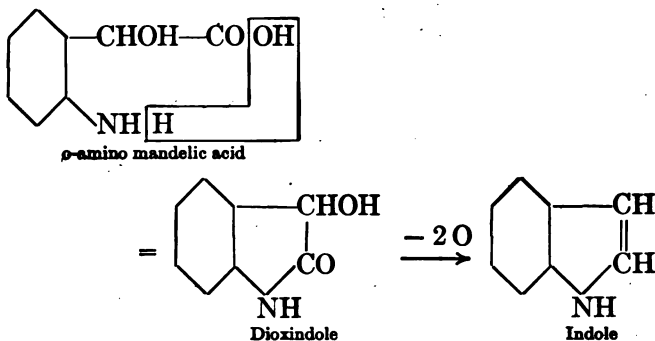
Both quinoline and isoquinoline are constituents of alkaloids.

## INDOLE AND ITS DERIVATIVES

**223. Indole** is a compound which contains a condensed benzene and a pyrole ring, the two having two ortho-carbon atoms in common. It is found in coal tar and is a constituent of one of the important amino acids contained

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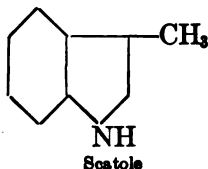
in proteins. *o*-amino mandelic acid is converted by the elimination of water into dioxindole, from which by vigorous reduction indole is formed :



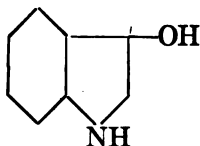
Indole is crystalline and melts at 52°. It has a fecal-like odor, and is volatile with steam. It is soluble in various organic solvents.

It is the complex which gives the red color with sulphuric acid and glyoxylic acid (Hopkins and Cole's reagent) which is characteristic of many proteins.

**224. Methyl Indole, or Scatole,** is found in putrefaction mixtures and in feces, where it results from tryptophane, one of the amino acids :

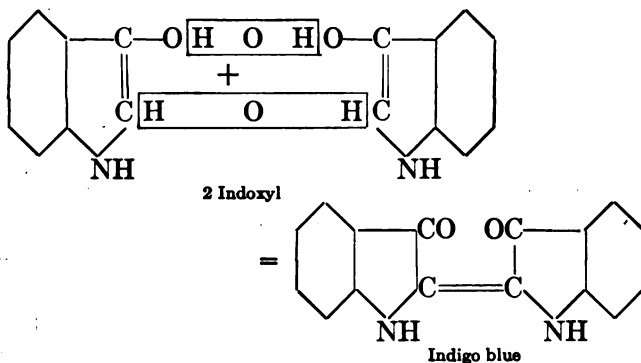


**225. Indoxyl** occurs in *Isatis tinctoria* as a glucoside, *indican*.

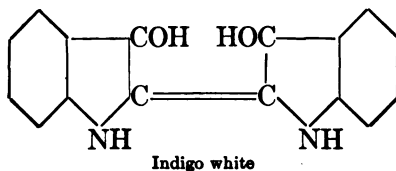


This is hydrolyzed by an enzyme in the plant and the free indoxyl undergoes oxidation to the blue dye *indigo*. Indoxyl is a product of the putrefaction of tryptophane and is formed in the intestine from proteins and being absorbed is eliminated in the urine, principally as indoxyl sulphuric acid, which is analogous to phenol sulphuric acid (180) in its constitution. The formation of indigo is the basis of the *indican* reaction of urine.

#### 226. Indigo:



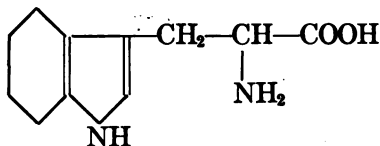
Indigo white is a reduction product of indigo blue:





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227. Tryptophane, or  $\alpha$ -amino,  $\beta$ -indolepropionic acid, is



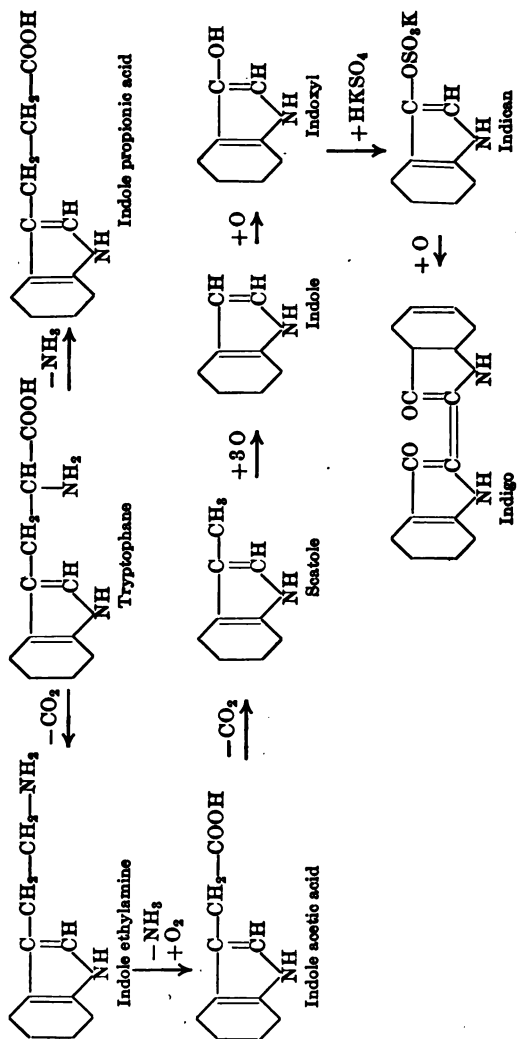
a constituent of many proteins. It is the complex which gives Adamkiewicz's reaction for proteins (Hopkins-Cole reaction).

It is a colorless crystalline compound readily soluble in hot water, but difficultly soluble in cold. Insoluble in absolute alcohol and in ether. It is soluble in hot pyridine. It melts at  $252^{\circ}$  after becoming brown at  $240^{\circ}$ . It is a weak base and forms salts with acids. Some of its acyl derivatives formed by the action of acid chlorides are of experimental value because of their properties. Tryptophane is destroyed in the hydrolysis of proteins by mineral acids, but is stable to barium hydrate.

Tryptophane gives a red color when a trace of bromine is added to its solutions acid with acetic acid. With concentrated sulphuric acid and glyoxylic acid it gives a reddish violet color.

Persons suffering from melanotic tumor excrete a pigmented substance called melanin in the urine. It has been rendered highly probable that the tryptophane complex in the protein molecule is the chief precursor of melanin in such subjects.

The more important products resulting from tryptophane in biological processes are represented by the following transformations:



## CHAPTER XXI

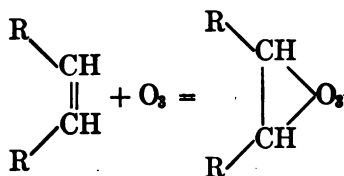
### THE TERPENES

**228.** Many of the volatile oils of plants are esters, but others which are contained especially in the flowers and stems of various coniferae consist of hydrocarbons of several types and their derivatives. These are grouped together as terpenes. Turpentine consists of a mixture of these, some liquid and holding in solution the solid forms. On distilling with steam the lighter members pass over, and the solid residue remaining behind is *colophony*.

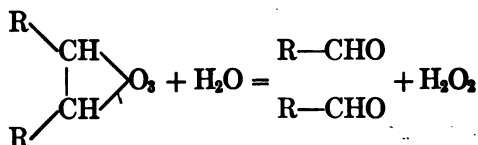
Most of the terpenes correspond to the formula  $C_{10}H_{16}$ . They are with few exceptions unsaturated, and are colorless, highly refractive liquids, boiling between  $155^{\circ}$  and  $180^{\circ}$ . Camphene is, however, a solid. They can be distilled with steam and have pleasant odors. They are soluble in many organic solvents, but not in water. The terpenes dissolve sulphur, phosphorus, iodine, rubber, and resins, and are much employed as solvents in varnishes, paints and in the arts. In most cases they contain one or more asymmetric carbon atoms and are therefore optically active, since, generally speaking, but one form occurs in nature. There are a few instances in which both optical forms occur naturally. They are easily decomposed by acids.

The terpenes yield addition products with nitrosyl chloride. From this on heating with alcoholic potassium

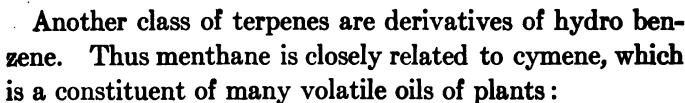
hydroxide HCl is split off, leaving a nitroso compound. They add on ozone at the points of double linkage, forming ozonides of the general type :

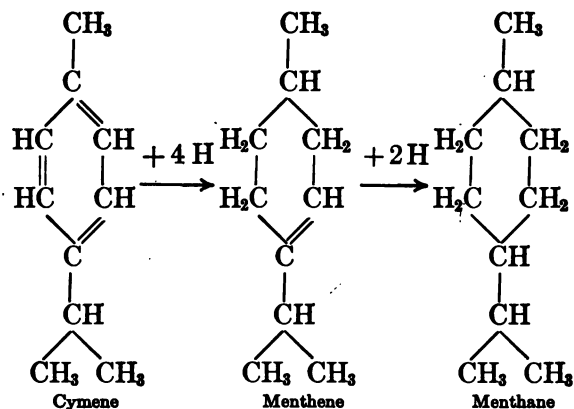


The ozonides on treatment with water are decomposed into aldehydes :

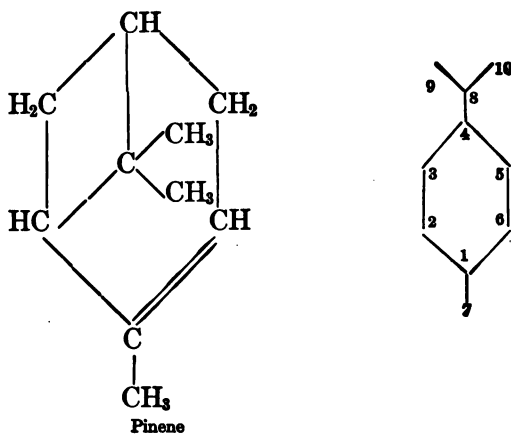


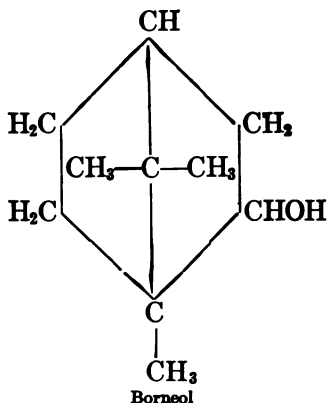
The terpenes by virtue of their unsaturated character form addition products with halogens. On reduction they are converted into hydroterpenes. On exposure to air they are oxidized to resins. They polymerize also to form resins. On oxidation with potassium permanganate they are in many cases oxidized to benzene derivatives. The terpenes may be considered as derived from hydrocarbons of the composition  $\text{C}_5\text{H}_8$ , of which isoprene (82) is an example. Two or more molecules of this substance can polymerize to form in the first instance a hydrocarbon,  $\text{C}_{10}\text{H}_{16}$ , or to a polyterpene,  $(\text{C}_5\text{H}_8)_n$ , of unknown molecular weight. The compounds of this series found in nature warrant the classification :





In certain cases it is necessary, in order to account for all the facts, to assign still more complex structures to individual terpenes. Thus *pinene*,  $\text{C}_{10}\text{H}_{16}$ , is believed to have the structure:





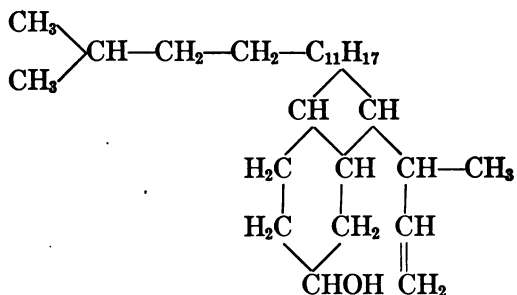
Assuming the skeleton illustrated and a union between carbon atoms 2 and 8, pinene consists of a six-membered and a four-membered ring. *Borneol* is believed to have a union between 8 and 1, giving the formula shown above.

d-pinene is the chief constituent of turpentine from America, Algeria, and Greece, while that from France and Spain is l-pinene. d-borneol is found in the product from Borneo and Sumatra.

Camphor is a sesquiterpene from the camphor tree. It is now made from pinene by oxidation. It differs from pinene in containing a ketone group.

**229. The Cholesterols** are closely related to the terpenes. While they resemble the hard fats in their physical properties, they differ from these in their remarkable stability toward oxidation. Micro-organisms do not attack them and they appear to be formed in every cell for protective purposes, and they play an important rôle in the living protoplasm by reason of their peculiar physi-

cal properties. The structure of cholesterol is not entirely known, but Windaus assigns to it the following partial provisional constitution :



The nature of the complex  $\text{C}_{11}\text{H}_{17}$  is entirely unknown. The properties of cholesterol have already been described (99).

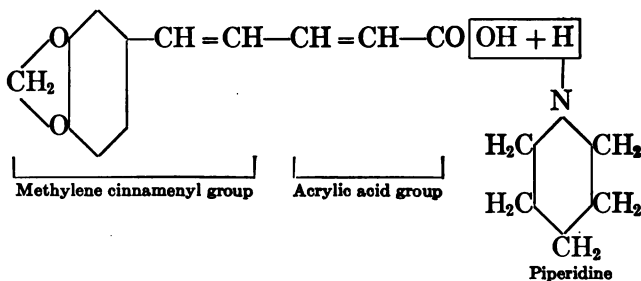


## CHAPTER XXII

### THE ALKALOIDS

The term alkaloid now includes those basic substances occurring in plants which are derived from pyridine, quinoline, isoquinoline, tropaine, or pyrrolidine.

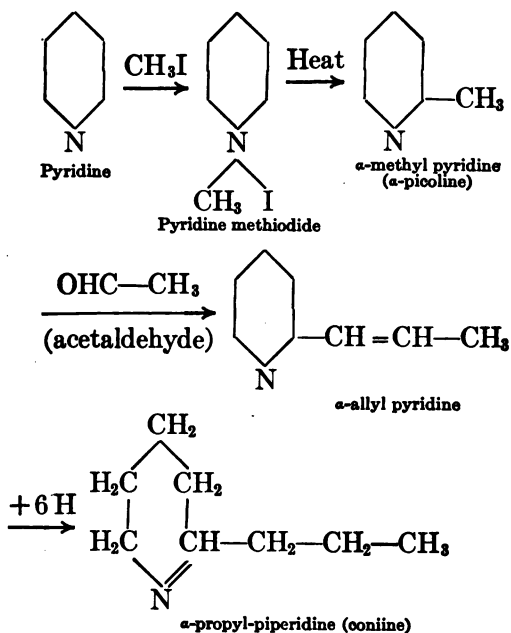
**230. Piperine**,  $C_{17}H_{19}NO_3$ , is a derivative of pyridine. On hydrolysis it yields piperidine and an acid, *piperic acid*, which may be regarded as the methylene ester of cinnamylacrylic acid :



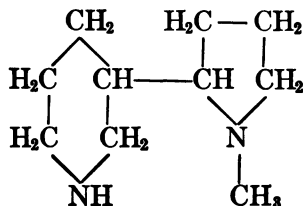
Piperine is a white solid substance melting at  $128^\circ$ . It does not dissolve in water, but is soluble in alcohol and ether. Black pepper contains about 8 per cent of this alkaloid.

**231. Coniine**,  $C_8H_{17}N$ , is the poisonous principle of the hemlock. It is dextrorotatory  $\alpha$ -n-propylpiperidine. It is a strong base which distills with steam when the seeds

of hemlock are distilled with sodium hydroxide. It was the first of the alkaloids to be synthesized. The steps by which Ladenburg accomplished this are as follows:



**232. Nicotine**,  $\text{C}_{10}\text{H}_{14}\text{N}_2$ , contains both a piperidine and a pyrrolidine ring. It is a colorless oily substance which

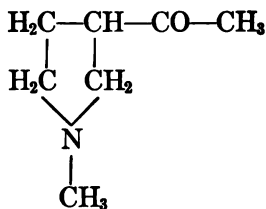


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boils at  $247^{\circ}$  and has an unpleasant smell and an extremely burning taste. Naturally occurring nicotine is levorotatory. The synthetic product is inactive, and d-nicotine has been prepared from it and from the natural product after racemization. The physiological effects of the natural form are twice as pronounced as are those of the optical isomer d-nicotine. It is extremely poisonous.

The alkaloids are not found generally distributed in plants, but certain ones are produced only by particular plant groups. The formation of pyrrolidine from tetramethylene diamine (117) and piperidine from pentamethylene diamine (320) give a clue to their mode of formation in the metabolism of the plant. These are formed from ornithine and lysine respectively, both of which amino acids occur in the course of protein decomposition. The formation of alkaloids is doubtless closely associated with the protein metabolism of the plant.

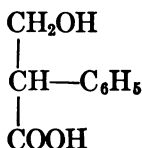
**233. Hygrine**, an alkaloid found in coca leaves, is  $\beta$ -acetyl-N-methyl pyrrolidine :



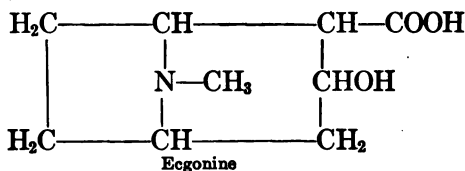
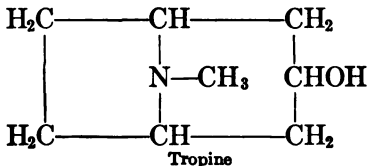
**234. Atropine and Hyoscyamine** differ chemically only in respect to their optical properties, the former being the d,l- and the latter the l-hyoscyamine. Atropine is found in the deadly nightshade and in henbane, and

hyoscyamine in the Jamestown weed, *Datura stramonium*. It is a white crystalline substance melting at  $115^{\circ}$ , readily soluble in alcohol, ether, and chloroform, but sparingly soluble in water. It is one of the most poisonous substances known.

On hydrolysis atropine yields tropic acid and tropine. Tropic acid has been shown to be  $\alpha$ -phenyl- $\beta$ -hydroxy propionic acid:



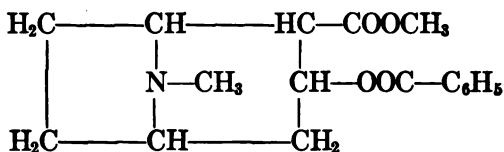
Tropine is made up of two condensed rings, one with five members, the other with six, a nitrogen atom serving as a "bridge."



Atropine is the ester of tropic acid with the secondary alcohol tropine.

**235. Cocaine**,  $\text{C}_{17}\text{H}_{21}\text{NO}_4$ , is an alkaloid in coca leaves. It is crystalline and melts at  $98^{\circ}$ . On hydrolysis it yields methyl alcohol, benzoic acid, and ecgonine. Its formula is:

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**236. Cinchonine**,  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ , present with *quinine* in cinchona bark, yields cinchonic acid or quinoline carboxylic acid and a piperidine derivative.

The structure of quinine is similar but is not known with certainty. It yields both quinoline and pyridine derivatives on hydrolysis.

**237. Strychnine**,  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ ; **Brucine**,  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$ , and **Curarine** are all present in the seeds of *Strychnos nuxvomica* and other plants of that family. They are all extremely poisonous. Strychnine yields both quinoline and indol on fusion with alkalis. The constitution of these alkaloids is not known.

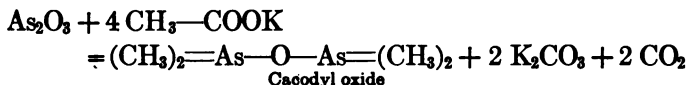
**238. Morphine**,  $\text{C}_{17}\text{H}_{19}\text{NO}_3$ , occurs in the juice of the poppy. There are a number of other alkaloids in the plant. Opium is the dried juice of the seed capsule of *Papaver somniferum*, a variety of poppy. It contains other alkaloids as well as a large number of substances such as fats, resins, proteins, sugars, inorganic salts, etc.

**239. Papaverine**, **Narcotine**, **Narceine**, **Laudanosine**, are all found in opium along with morphine. They are derivatives of isoquinoline.

## CHAPTER XXIII

### ORGANIC ARSENIC COMPOUNDS

**240. Cacodylic acid**,  $(\text{CH}_3)_2\text{AsO—OH}$ . This organic arsenic derivative is formed when potassium acetate is distilled with arsenic trioxide. The principal reaction is represented by the following equation:



The distillate is an oily liquid with an overpowering odor and extremely poisonous properties. The radical  $\text{—As}(\text{CH}_3)_2$  corresponds to  $\text{—N}(\text{CH}_3)_2$ . In the distillate is also a substance called cacodyl:

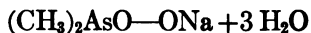


Cacodyl and its homologues are analogous to the substituted hydrazines  $\text{R}_2\text{=N—N=R}_2$ .

Cacodyl oxide when treated with hydrochloric acid yields cacodyl chloride:



Both cacodyl and cacodyl oxide are converted into cacodylic acid by oxidation. The most important salt is the sodium salt, which has been much used in medicine. It corresponds to the formula



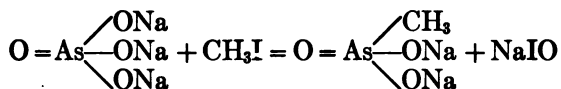
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This salt is a white crystalline powder which dissolves readily in water. It is much less poisonous than are the salts of arsenious acid.

**241. Arrhenal**, sodium methyl arsenate,

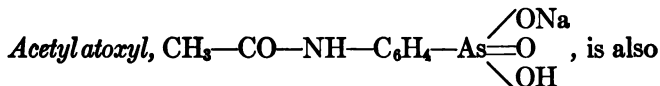
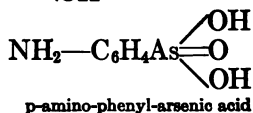
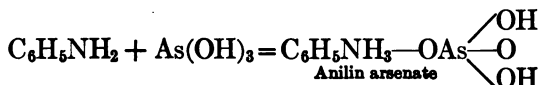


is formed by the action of methyl iodide on sodium arsenate in alkaline solution :



The great stability of these arsenic derivatives containing aliphatic radicals, and the correspondingly slight arsenical effect which follows their administration, has led to the substitution in great measure of aromatic arsenic compounds in medicine.

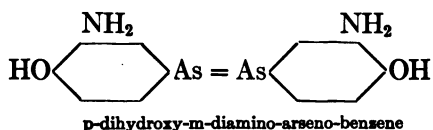
**242. Atoxyl**, sodium *p*-amino-phenyl-arsenate, is formed when aniline and arsenic acid are heated together. As an intermediate product, aniline arsenate, is formed :



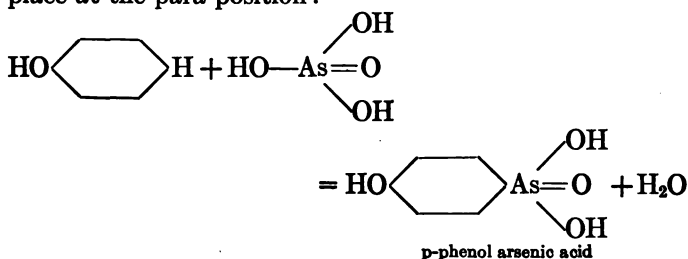
Acetyl atoxyl

employed as a compound for the slow administration of arsenic in medicine.

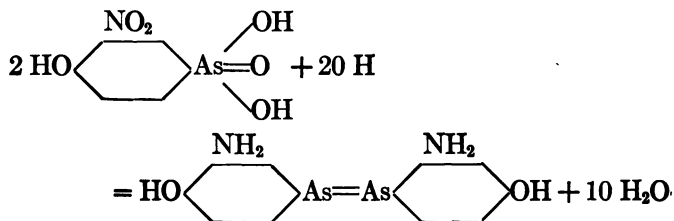
**Salvarsan**, an arsenic compound having a peculiar specific toxic effect upon the protozoa causing syphilis, is one of the most valuable remedies yet discovered. It is *p*-dihydroxy-*m*-diamino-arseno-benzene. The following reactions illustrate its preparation :



On heating phenol with arsenic acid, condensation takes place at the para position :



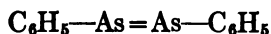
On nitration this yields a nitro derivative having the  $\text{—NO}_2$  group in the *o*- position to the  $\text{—OH}$ . On complete reduction of this compound the nitro group is converted into an amino group and the oxygen is removed from the arsenic acid group, the two residues are condensed :





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Salvarsan is a derivative of arseno-benzene,



which is analogous to azo benzene :  $\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_5$ .

### THE PROTEINS

**243.** The proteins form a very important group of substances which constitute the greater part of the solids of animal tissues and are present in all tissues of both animal and plant origin. Typical proteins are the white of egg, casein of milk, which is the part separated in the curdling of milk, hair, nails, silk, etc.

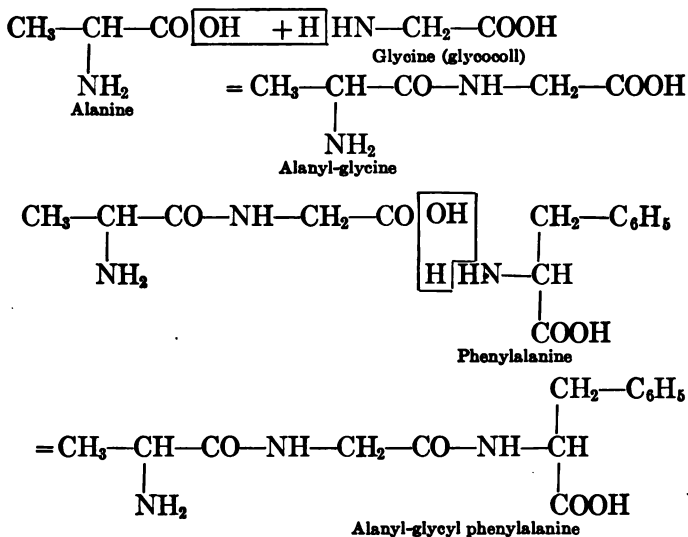
Chemically the proteins are made up of amino acids; seventeen of these, glycocoll, alanine, valine, leucine and isoleucine, phenylalanine, tyrosine, serine, cystine, proline, oxyproline, aspartic acid, glutaminic acid, arginine, lysine, histidine, and tryptophane have been isolated and identified. These have all been described in this book. It is possible that there are others as yet unidentified.

The proteins differ most widely in their physical properties, some being soluble in water (albumins), others insoluble in water, but soluble in dilute salt solutions (globulins), others insoluble in both these solvents, but soluble in dilute acids or alkalies (glutelins). There is a class called prolamines, which are especially abundant in wheat, rye, barley, and maize, which are insoluble in water or salt solutions, but dissolve readily in 70–80 per cent alcohol.

Nearly all proteins contain sulphur, and a few also contain phosphorus; the latter occur only in milk and in eggs.

Simple proteins on hydrolysis with mineral acids yield only  $\alpha$ -amino acids. The structure of the proteins has been made clear by the work of E. Fischer, who has produced numerous synthetic products closely similar to the natural.

The proteins consist of amino acids in "peptide" union with each other. This union results from the interaction of the carboxyl group of one with the  $\alpha$ -amino group of another :



Such complexes are called di-, tri-, tetra-, etc. peptides according to the number of amino acid molecules which they contain. The number of compounds which it is possible to form from seventeen amino acids arranged in different orders is extremely great and readily accounts for the very numerous proteins found in the plant and animal world.

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Proteins are known which consist of the three diamino acids arginine, lysine, and histidine, and arginine in one instance constitutes about 85 per cent of the total nitrogen content. These are termed *protamines* and occur only in the heads of the spermatozoa of animals.

Proteins differ greatly in the proportions of the different amino acids which they yield. Glutamic acid occurs to the extent of 40 per cent in certain of the wheat proteins (gliadin) and as little as 2 per cent in the globulin globin of the blood. Silk is more than half made up of peptide combinations of glycocoll and alanine. Tryptophane, tyrosine, and cystine are all lacking from gelatin, derived by the incipient hydrolysis of connective tissue, the organic matrix of bones, etc. A few yield no glycocoll.

In digestion by enzymes such as pepsin or trypsin the peptide linkages are broken, the elements of water being taken up to form an amino and a carboxyl group, *i.e.* digestion is the reverse of the process described in the formation of the peptides.

### THE CONJUGATED PROTEINS

The proteins also exist in nature in certain instances in union with other substances as phosphoric acid (phosphoproteins), glucosamine (glycoproteins), nucleic acids (nucleoproteins), etc.

The chemistry of the proteins is so extensive and involves a consideration of their physical properties as *colloids*, as well as their chemical constitution, that it properly belongs in the special branch of physiological chemistry and will not be further dealt with here.

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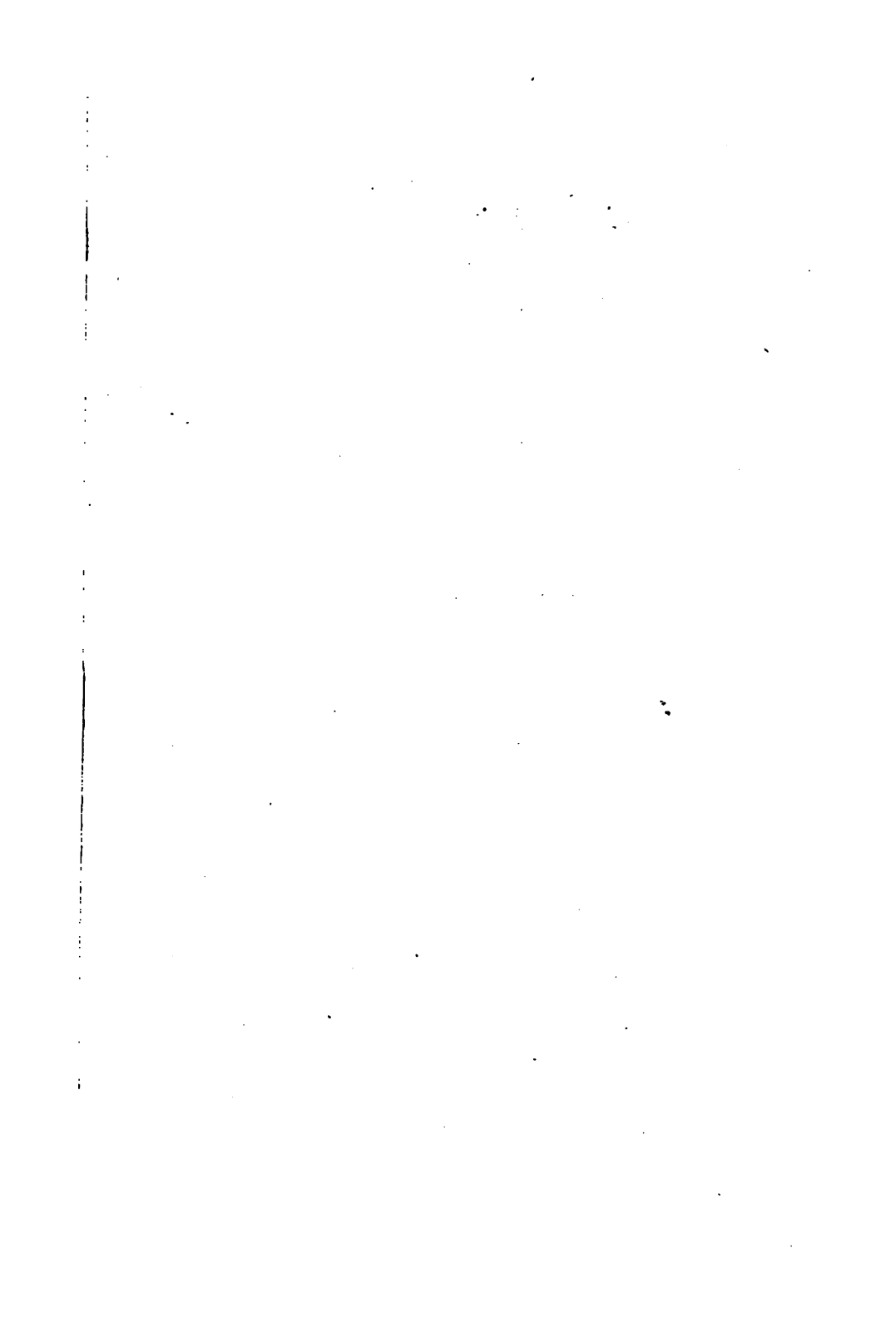
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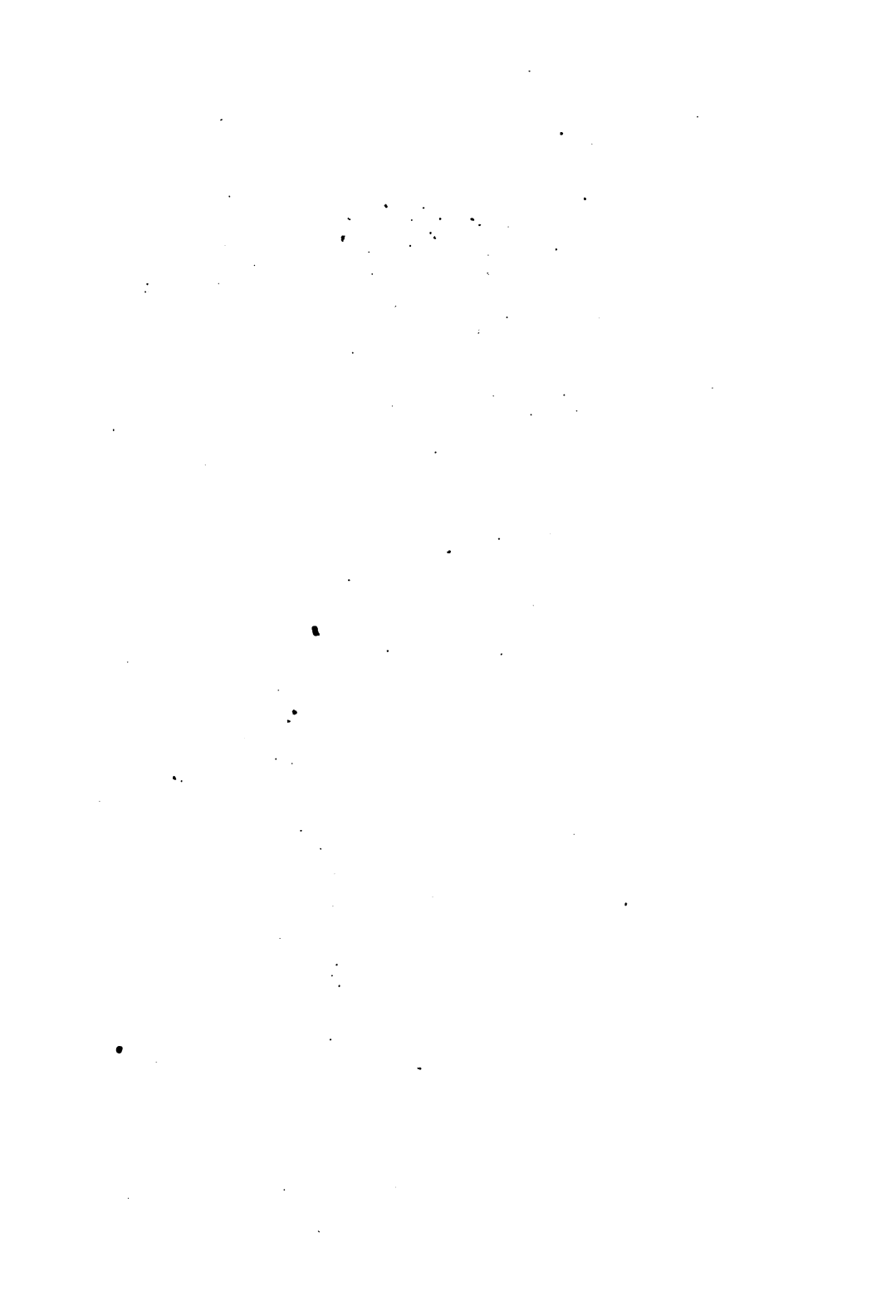
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